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Original Articles

STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. I*

Introduction. The Demand for and Requirements of a Standardized Wassermann Reaction and Method of Investigation

By JOHN A. KOLMER, M.D., Philadelphia, Pa.

From the McManes Laboratory of Experimental Pathology of the University of Pennsylvania, and the Dermatological Research Laboratories of the Polyclinic

(Received for publication, November 9, 1918)

PROBABLY no laboratory test has been subject to as much favorable and unfavorable criticism and to as many modifications in technic as Wassermann's serum test for syphilis; owing to the fact that the reaction is not strictly or biologically specific for syphilis and requires several biological reagents of varying properties, it is readily subject to error in both a positive and negative way unless carefully and intelligently understood and conducted, and largely for these reasons has fallen into disrepute with many physicians and surgeons.

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*Presented before the Fourth Annual Meeting of the American Association of Immunologists, New York, May, 1917.

Many of the proposed modifications of the original technic have been demanded by an increasing experience and knowledge of the reaction and several have undoubtedly served to improve its delicacy and value, but the employment of different methods by various persons has led to wide variation in the results, confusion in regard to the actual value of the test and insistent demand for one standard method.

Within recent years several publications have drawn particular attention to discrepancies in the results of Wassermann reactions with the same serum in different laboratories and indeed, to varying results reported by the same serologist on specimens of blood from the same individual withdrawn at the same time and under identical conditions. For example, Uhle and MacKinney[1] who submitted specimens of blood from each of 292 individuals to from four to ten laboratories, found that "there is one chance in five that the tests will agree;" Phelps[2] in a similar analysis of the results of Wassermann tests with 358 specimens of blood divided and sent to from two to four laboratories, found that the results agreed in but from 52 to 65 per cent and Wolbarst[3] in a study of 37 cases by two or more serologists, found that the results agreed in 70 per cent and disagreed either slightly or absolutely in 30 per cent.

I believe all serologists of experience agree that a certain percentage of discrepancies are to be expected with the use of different hemolytic systems and reagents and particularly different antigens, even granting that all tests were conducted with the requisite technical care and attention to details; I do not know the legal value of the Wassermann reaction, but I surmise that the testimony of several serologists under close cross-examination upon the witness stand would bid fair to outshine the exhibition of alienists in regard to conflicting statements. But the Wassermann reaction is only one of numerous laboratory tests requiring standardization to increase value and reliability; for example, it is well known that the much simpler Widal reaction may yield varying results in different laboratories with portions of the same specimen of blood and indeed, conflicting reports on the results of urinalysis with portions of the same specimen of urine containing traces of albumin or sugar, may be expected. Nevertheless, it is the overwhelming consensus of opinion that the Wassermann reaction possesses great value in the diagnosis of syphilis and as a serologic guide to treatment, owing largely to the fact that the individual physician has learned to rely upon the work of at least one of his colleagues, but, owing to the nature and importance of the disease to the individual and community, standardization of the technic for the serum diagnosis of syphilis is especially desirable in order to increase the delicacy and reliability of the reaction. All of the above mentioned authors in addition to Pusey,[4] Shropshire,[5] and others have emphasized the need of a standardized technic; Brem,[6] Faller,[7] Schlesinger,[8] and numerous others have directed attention to sources of error in the technic, while Vedder,[9] and Ottenburg,[10] have made valuable and notable contributions upon the subject of standardization to which further reference will be made.

SOURCES OF ERROR IN THE WASSERMANN REACTION

As is now well known there are many sources of error in the technic of the Wassermann reaction; more, probably, than in any other practical everyday test being employed. These sources of error may be (a) *unavoidable* and (b) *avoidable*. By *unavoidable* sources of error I refer to that change occurring in the serums of persons suffering with diseases other than syphilis, as frambesia (yaws) and leprosy, which are said to be responsible for positive Wassermann reactions in the absence of syphilis under rigidly correct technical conditions. In frambesia the reason is readily surmised inasmuch as the etiologic agent is a spirochete bearing some resemblance to Treponema pallidum and like the latter, highly vulnerable to the spirocheticidal action of arsenobenzol. A review of the literature on the Wassermann reaction and particularly the earlier papers, shows that positive reactions have been reported by some one at some time in practically all diseases to which human flesh is heir, but we now know that many of these reports must have been due to *avoidable* errors in technic. Scarlet fever, for example, is one disease which writers persist in handing down as yielding falsely positive Wassermann reactions; I am sure this is an error and believe that further investigations will reduce the diseases in which falsely positive reactions are said to occur, although it is realized at present that certain and unknown changes in the colloidal chemistry of the body fluids in the presence of fever, acidosis, uremia, et cetera, may introduce an unavoidable source of error in the Wassermann reaction which, however, in those places where yaws is unknown and leprosy uncommon, is very slight indeed.

By *avoidable* sources of error, I refer to those present in the various biological reagents of the test, as in complement, hemolysin and particularly the antigen; likewise to errors due to careless technic. A standardized method aims to detect and avoid all avoidable errors although it can not account for the personal equation of the individual serologist in regard to exactness in work, beyond making the test and the method of reading the results as simply, definitely and clearly as possible.

REQUIREMENTS OF A STANDARD WASSERMANN REACTION

In our studies upon this subject we have had the following six main requirements in mind:

1. *Practical specificity* as sought by efforts toward removing all avoidable sources of error.

2. *Sensitiveness or as much delicacy as is permissible with specificity;* we are of the opinion that the Wassermann reaction as ordinarily conducted is not too sensitive but not sensitive enough and have worked on this basis. It is an easy matter to secure positive reactions in secondary syphilis and paresis when the serum or cerebrospinal fluid or both are laden with the Wassermann antibody, but a technic to be worth while must be able to detect latent syphilis and to demonstrate so far as specifically possible the last traces of spirochetic life and activity in a person under treatment; the studies of Warthin[11] have demonstrated the great deal which should be required theoretically of the Wassermann reaction in this direction, inasmuch as this investigator found spirochetes in the tissues of numerous syphilitics yielding negative Wassermann reactions during life.

3. *Uniformity in results;* a standard method should aim to fulfill the following requirements in this direction: (a) yield similar results in the same laboratory when the serologist or serologists are working with portions of the same specimen of blood submitted under fictitious names as specimens from different persons; (b) yield similar results insofar as positive or negative are concerned at least, when portions of the same blood are sent to different laboratories in the same city or to outside places not further removed than one day's travel; (c) yield approximately similar results on the degree of posi-

tiveness with syphilitic serums in the same laboratory and in different laboratories. As stated above under *b* the same and different laboratories should agree at least upon whether a serum yields a positive or negative reaction; in my experience most variation occurs with serums yielding weakly positive reactions. Slight discrepancies in the reports on the degree of complement fixation must be expected, inasmuch as the personal equation plays an important part in reading the degree of hemolysis, as it does in matching colors in other lines of work, for example, in hemoglobin estimations and color reactions in general. Slight discrepancies, however, do no harm as long as the primary question of whether a serum does or does not yield a positive or negative result is untouched and particularly with serums yielding the borderline weakly positive or doubtfully negative reactions.

4. *Quantitative:* Now that the Wassermann reaction is known to be influenced by treatment and is widely employed as a therapeutic guide, a standard technic should be able to measure the degree of complement fixation and indicate the influence of treatment with considerable accuracy.

5. *Simplicity* is important inasmuch as it tends to greater accuracy. Simplicity, however, is but a relative term inasmuch as the simplest technic is a complicated problem for the unexperienced and insufficiently trained worker, whereas a more complicated technic is perfectly simple to the experienced serologist. Simplicity of technic, however, aims to open up the test to a larger number of persons, but should never be sought at the expense of accuracy and sensitiveness.

6. *Economy* is of special importance in laboratories conducting a large number of tests. The only factor, however, of special importance in this connection is guinea pig serum for complement inasmuch as antigen and hemolysin are readily prepared in large amounts and patient's serum and erythrocytes for hemolytic system, easily secured.

METHOD OF INVESTIGATION

Realizing the complex nature of the Wassermann reaction and the variable properties of its several biological reagents, our almost complete ignorance of its mechanism and the absence of a specific and wholly satisfactory antigen, the task of even attempting standardization was considered a serious and laborious problem; knowing that the majority of serologists had an individual way of conducting certain steps in the technic and particularly that many had learned from experience to rely so firmly upon their own method as to be very loath to accept any other, the hope of building up a widely acceptable technic would appear almost hopeless unless an unexpected discovery bestowed upon the standard technic an indisputable quality of excellence. The method pursued in this investigation, which has covered a period of several years, was to become acquainted with all existing methods by thoroughly reviewing the available literature and by means of personal communications and interviews with a large group of serologists and *submitting the whole to careful unbiased experiment* and choosing that proving best on the basis of actual trial and receiving endorsement on the basis of experience from other serologists. In this manner, we have evolved a technic built up on the experience of others in addition to our own, embracing some original methods and a new antigen, which we hope will at least stimulate a proportion of serologists to give the method a trial and thereby aid in arriving at a conclusion regarding its status as an acceptable standard technic for the Wassermann reaction.

ACKNOWLEDGMENTS

This investigation was instituted in the McManes Laboratory of Experimental Pathology of the University of Pennsylvania in 1915 with financial aid generously subscribed by Dr. Alexander Uhle and Dr. William H. MacKinney of Philadelphia, both of whom have used the Wassermann reaction in a large practice and have learned on the basis of practical experience and investigation the shortcomings of the reaction and the need for an acceptable standard technic; since the lamentable death of Dr. Uhle, Dr. MacKinney continued his financial aid until the work was shared by the Dermatological Research Laboratories of the Polyclinic, and it is a great pleasure to gratefully acknowledge their aid and cooperation.

I am also indebted to Dr. Toitsu Matsunami of the Imperial University of Tokyo, for his untiring, zealous, and valuable cooperation and assistance in conducting the major portion of experimental work; also to Dr. C. P. Brown, Dr. Berta Meine, Miss Mary E. Trist and others for suggestions, cooperation and valuable assistance.

SUMMARY

The variable nature of the Wassermann reaction with the same serums in the hands of different serologists as the basis for the demand for a standardized technic is discussed; also the sources of error in the Wassermann reaction which are divided into (1) avoidable and (2) unavoidable errors, and the requirements of a standard technic with the method of investigation pursued.

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STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. II*

THE PREPARATION OF GLASSWARE AND SALINE SOLUTION FOR THE WASSERMANN REACTION. THE INFLUENCE OF ACIDS, ALKALI, AND OTHER FACTORS

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(Received for publication, November 9, 1918)

THAT variable and erroneous results in the Wassermann reaction may occur from the use of improperly prepared glassware (test tubes, pipets and flasks) mainly due to the presence of traces of acid or alkali, is well known; doubtless this factor of error is removed in the majority of laboratories by proper methods of cleaning, but the subject is of sufficient importance to demand attention as a fundamental factor in the question of a standard technic isasmuch as sufficient amounts of these substances may be present in new glassware or after insufficient rinsing following cleaning with solutions of strong soaps and soap powders, dilute hydrochloric acid or bichromate cleaning fluid, to very materially influence reactions and particularly by a destructive action upon complement.

Hektoen and Ruediger[1] and Manwaring[2] have shown that many inorganic salts in small doses prevent hemolysis due to their action on the complements; Manwaring also found that many of these salts in various doses were hemolytic for dog erythrocytes. Cumming[3] found that a serum known to be Wassermann negative could be made to give a falsely positive reaction by the addition of a trace of either acid or alkali, and somewhat larger quantities of acid or alkali would cause a syphilitic serum to yield a negative result. Similarly neutral salts were found to influence a normal serum to the extent of causing a positive reaction although the converse of this was not true. In his experiments, hydrochloric acid in 0.0039 per cent in one cubic centimeter of 1 per cent suspension of sheep cells produced hemolysis in a period of fifteen minutes, and 0.0055 per cent produced lysis of a similar quantity of human cells; sodium hydroxide was less hemolytic, inasmuch as 0.024 and 0.0162 per cent was required to produce hemolysis of sheep and human cells respectively. Sherwood[4] has studied the antilytic action of various substances administered to living animals and also in vitro, finding that hydrochloric acid and other substances were markedly antilytic.

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*Presented before the Fourth Annual Meeting of the American Association of Immunologists, New York, May, 1917.

EXPERIMENTAL

The purposes of our experiments were as follows:

1. To study the influence of alkalies (sodium hydroxide) and acids (hydrochloric acid; bichromate cleanser*) upon red blood cells alone, serum hemolysis and the Wassermann reaction; also similar studies upon the influence of new and unwashed and dirty glassware.

2. Since it is the custom in some laboratories to use one pipet for different serums depending upon washing the pipet once or more with salt solution to avoid error, we have studied experimentally the possibility of this method being responsible for positive reactions with normal serum by reason of carrying over traces of a preceding positive serum.

3. The one solution employed in the Wassermann test is a 0.7 to 0.9 per cent solution of sodium chloride in water (physiologic saline solution). Inasmuch as previous investigations mentioned above have shown that minute amounts of various salts may prove anticomplementary, we have included experiments with saline solutions prepared of ordinary table salt and chemically pure sodium chloride in a constant percentage of 0.85 in tap water and freshly distilled and stale (commercial) distilled water.

METHOD OF STUDY

All of our experiments were conducted with 2.5 per cent suspensions of fresh and triply washed sheep cells in dose of 1 c.c.; in the hemolytic and Wassermann tests complement was furnished by the mixed serums of guinea pigs in constant dose of 1. c.c. 1:20 dilution; antisheep hemolysin was titrated with each complement serum and corpuscle suspension and used in a dose corresponding to 2 units.

In the experiments with alkalies and acids, varying dilutions of normal solutions of sodium hydroxide and hydrochloric acid were prepared with physiologic saline solution (0.85 per cent C.P. sodium chloride in distilled water) and used in amounts of one cubic centimeter; the total volume in each tube after the addition of cells, etc., varied from 2 to 2.5 c.c., being considered sufficiently accurate for the simple purposes of the experiments.

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*Bichromate cleaning fluid is prepared of 2 parts potassium bichromate; 3 parts commercial sulphuric acid, and 25 parts water.

In the experiments bearing upon the hemolytic activity of the various substances, 1 c.c. of the 2.5 per cent suspension of sheep cells were added to 1 c.c. of varying dilutions, mixed and incubated at 38° C. in a water-bath, when the results were read.

In the experiments bearing upon the influence of various substances upon serum hemolysis and the Wassermann reaction, the primary incubation in the water-bath was of thirty minutes duration followed by the addition of two units of hemolysin and 1 c.c. of 2.5 per cent suspension of sheep cells and reincubation for one-half hour, when the results were read.

TABLE I

INFLUENCE OF SODIUM HYDROXIDE UPON RED BLOOD CORPUSCLES AND SERUM HEMOLYSIS

NORMAL SODIUM HYDROXIDE			HEMOLYTIC SYSTEM			RESULTS	
Dilutions	Dose	Approx. Amt. Pure NaOH (gm.)	Complement 1:20	Hemolysin 1:1000	Cells 2½%	Influence upon Cells Alone	Influence upon Serum Hemolysis
$\frac{N}{1}$	1 c.c.	0.04	1 c.c.	2 units	1 c.c.	C.H.*	C.H.
1:10	“	0.004	“	“	“	“	“
1:100	“	0.0004	“	“	“	“	N.H.**
1:200	“	0.0002	“	“	“	N.H.	“
1:300	“	0.00013	“	“	“	“	“
1:400	“	0.0001	“	“	“	“	S.H.***
1:500	“	0.00008	“	“	“	“	C.H.
1:600	“	0.000066	“	“	“	“	“
1:700	“	0.000055	“	“	“	“	“
1:800	“	0.00005	“	“	“	“	“
1:900	“	0.000044	“	“	“	“	“
1:1000	“	0.00004	“	“	“	“	“
Control	0	0	“	“	“	0	“

*C.H. = Complete hemolysis.
**N.H. = No hemolysis.
***S.H. = Slight hemolysis.

RESULTS

(A) The Influence of Sodium Hydroxide, Hydrochloric Acid and Bichromate Cleaning Fluid (Potassium Bichromate and Sulphuric

Acid) upon Sheep Cells Alone, Serum Hemolysis and the Wassermann Reaction. The results of a few experiments are shown in Tables I-IX as illustrative of those observed and may be summarized as follows:

1. Approximately 1 c.c. of a 1:100 dilution of normal sodium hydroxide (about 0.0004 gm.) in a total volume of 2 c.c. was sufficiently hemolytic to almost completely destroy 1 c.c. of a 2.5 suspension of washed sheep cells; a much lesser amount, namely, 1 c.c. of a 1:400 dilution (about 0.0001 gm. sodium hydroxide) served to interfere with serum hemolysis and presumably by a destructive action upon complement (Table I).

2. In the Wassermann reaction with known normal or negative serum, 1 c.c. of 1:400 and 1:500 dilutions of normal sodium hydroxide (approximately 0.0001 to 0.00008 gm.) proved sufficiently antilytic to interfere with hemolysis and yield falsely positive results; a similar anticomplementary influence was noted in the antigen, serum and hemolytic controls although the amounts of alkali were too small to hemolyze the cell alone (Table II). Similar results were observed in experiments with a syphilitic serum, that is, the alkali in these minute amounts proved antilytic by a destructive influence upon the complement (Table III).

TABLE II

INFLUENCE OF SODIUM HYDROXIDE UPON THE WASSERMANN REACTION WITH NORMAL SERUM

DILUTION OF NORMAL NaOH 1 C.C.	APPROX. AMT. PURE NaOH (GM.)	INFLUENCE UPON				
		WASS. REACT.*	ANTIGEN CONTROL	SERUM CONTROL	HEMOLYTIC CONTROL	CORPUSCLE CONTROL
1:400	0.0001	++**	++	+	+	N.H.***
1:500	0.00008	–	–	–	±	"
1:600	0.000066	–	–	–	–	"
1:700	0.000055	–	–	–	–	"
1:800	0.00005	–	–	–	–	"
1:900	0.000044	–	–	–	–	"
1:1000	0.00004	–	–	–	–	"

*Conducted with an extract of acetone-insoluble lipoids as antigen.

**++ = 50 per cent inhibition of hemolysis (moderately positive); + = 25 per cent inhibition (weakly positive); ± = 10 per cent inhibition (very weakly positive); – = complete hemolysis.

***N.H. = No hemolysis.

3. Similar results were observed with hydrochloric acid except in a more marked degree inasmuch as the acid proved more lytic for

TABLE III

INFLUENCE OF SODIUM HYDROXIDE UPON WASSERMANN REACTION WITH SYPHILITIC SERUM

DILUTIONS OF NORMAL NaOH 1 C.C.	APPROX. AMT. PURE NaOH (GM.)	INFLUENCE UPON				
		WASS. REACT.*	ANTIGEN CONTROL	SERUM CONTROL	HEMOLYTIC CONTROL	CORPUSCLE CONTROL
1:400	0.0001	++++**	++	++	+++	N.H.
1:500	0.00008	++++	+	+	++	"
1:600	0.000066	++++	–	–	+	"
1:700	0.000055	++++	–	–	–	"
1:800	0.00005	++++	–	–	–	"
1:900	0.000044	++++	–	–	–	"
1:1000	0.00004	++++	–	–	–	"

*Conducted with an extract of acetone-insoluble lipoids; water-bath incubation.

**++++ = 100 per cent inhibition of hemolysis, or strongly positive; +++ = 75 per cent inhibition, or moderately positive, etc.

the cells alone and more destructive for complement. As shown in Table IV amounts of acid as minute as 1 c.c. of a 1:300 dilution of a N/1 solution equivalent approximately to 0.000012 c.c. or about 0.000015 c.c. of the commercial (81 per cent) product proved hemolytic while 1 c.c. of a 1:500 dilution or approximately 0.000007 c.c. of pure acid or 0.000012 c.c. of the commercial acid, proved anticomplement-

TABLE IV

INFLUENCE OF HYDROCHLORIC ACID UPON RED BLOOD CORPUSCLES AND SERUM HEMOLYSIS

NORMAL HYDROCHLORIC ACID			HEMOLYTIC SYSTEM			RESULTS	
Dilutions	Dose	Approx. Amt. Pure acid c.c.	Complement 1:20	Hemolysin 1:1000	Cells 2½%	Influence upon Cells Alone	Influence upon Serum Hemolysis
$\frac{N}{1}$	1 c.c.	.00365	1 c.c.	2 units	1 c.c.	C.H.*	C.H.
1:10	"	.000365	"	"	"	"	"
1:100	"	.0000365	"	"	"	"	"
1:200	"	.000018	"	"	"	"	S.H.*
1:300	"	.000012	"	"	"	"	N.H.
1:400	"	.000009	"	"	"	N.H.	"
1:500	"	.0000073	"	"	"	"	M.H.*
1:600	"	.000006	"	"	"	"	C.H.
1:700	"	.0000052	"	"	"	"	"
1:800	"	.0000045	"	"	"	"	"
1:900	"	.000004	"	"	"	"	"
1:1000	"	.0000036	"	"	"	"	"
Control	0	0	"	"	"	0	"

*C.H. = Complete hemolysis; S.H. = Slight hemolysis; N.H. = No hemolysis; M.H. = Marked hemolysis.

ary. In the Wassermann reaction with normal and syphilitic serums 1 c.c. of 1:500 to 1:800 dilutions of normal hydrochloric acid (approximately 0.000007 to 0.0000045 c.c. pure acid) proved antilytic and yielded false positive results. (Tables V and VI.)

TABLE V

INFLUENCE OF HYDROCHLORIC ACID UPON WASSERMANN REACTION WITH NORMAL SERUM

DILUTION OF NORMAL HCL C.C.	APPROX. AMT. PURE ACID C.C.	INFLUENCE UPON				
		WASS. REACT.*	ANTIGEN CONTROL	SERUM CONTROL	HEMOLYTIC CONTROL	CORPUSCLE CONTROL
1:400	.000009	+	++	+	++	No hemolysis
1:500	.0000073	±	±	−	+	" "
1:600	.000006	−	−	−	−	" "
1:700	.0000052	−	−	−	−	" "
1:800	.0000045	−	−	−	−	" "
1:900	.000004	−	−	−	−	" "
1:1000	.0000036	−	−	−	−	" "

*Conducted with an antigen of acetone-insoluble lipoids.

TABLE VI

INFLUENCE OF HYDROCHLORIC ACID UPON WASSERMANN REACTION WITH SYPHILITIC SERUM

DILUTION OF NORMAL HCL 1 C.C.	APPROX. AMT. PURE ACID C.C.	INFLUENCE UPON				
		WASS. REACT.*	ANTIGEN CONTROL	SERUM CONTROL	HEMOLYTIC CONTROL	CORPUSCLE CONTROL
1:400	.000009	++++	++++	+	++++	N.H.**
1:500	.0000073	++++	++++	+	++	"
1:600	.000006	++++	++	−	−	"
1:700	.0000052	++++	++	−	−	"
1:800	.0000045	++++	+	−	−	"
1:900	.000004	++++	−	−	−	"
1:1000	.0000036	++++	−	−	−	"

*Conducted with an extract of acetone-insoluble lipoids; water-bath incubation.
**N.H. = No hemolysis.

4. The bichromate cleaning fluid proved even more hemolytic and anticomplementary due to the presence of larger amounts of sulphuric acid in addition to the presence of potassium bichromate, which is alone hemolytic and anticomplementary. As shown in Table VII amounts of this cleaning fluid as low as 1 c.c. of 1:600 dilution proved hemolytic, while even smaller amounts as 1 c.c. of a 1:900 dilution may prove antilytic due, presumably, to a destructive effect upon complement (Table VII).

TABLE VII

INFLUENCE OF BICHROMATE CLEANING SOLUTION UPON RED BLOOD CORPUSCLES AND SERUM HEMOLYSIS

BICHROMATE SOLUTION		HEMOLYTIC SYSTEM			RESULTS	
Dilutions	Dose	Complement 1:20	Hemolysin 1:1000	Cells 2½%	Influence upon Cells Alone	Influence upon Serum Hemolysis
Undiluted	1 c.c.	1 c.c.	2 units	1 c.c.	C.H.	C.H.
1:10	"	"	"	"	"	"
1:100	"	"	"	"	"	"
1:200	"	"	"	"	"	"
1:300	"	"	"	"	"	"
1:400	"	"	"	"	"	"
1:500	"	"	"	"	"	"
1:600	"	"	"	"	S.H.	"
1:700	"	"	"	"	"	"
1:800	"	"	"	"	N.H.	"
1:900	"	"	"	"	N.H.	M.H.
1:1,000	"	"	"	"	"	"
1:10,000	"	"	"	"	"	C.H.
1:100,000	"	"	"	"	"	"

5. In complement fixation reactions with normal and syphilitic serum 1 c.c. of a dilution of bichromate fluid as high as 1:300 proved anticomplementary and yielded falsely positive reactions. (Tables VIII and IX.)

TABLE VIII

INFLUENCE OF BICHROMATE CLEANING FLUID UPON WASSERMANN REACTION WITH NORMAL SERUM

DILUTION OF BICHROMATE SOL. C.C.	INFLUENCE UPON			
	WASS. REACT.*	ANTIGEN CONTROL	SERUM CONTROL	HEMOLYTIC CONTROL
1:200	++	+	++	++
1:300	+	±	+	+
1:400	–	–	–	–
1:600	–	–	–	–
1:800	–	–	–	–
1:1000	–	–	–	–
1:2000	–	–	–	–

*Conducted with an antigen of acetone-insoluble lipoids.

6. In Wassermann reactions with syphilitic serum, sodium hydroxide, hydrochloric acid and the bichromate cleaning fluid had less influence insofar as producing falsely negative results were concerned. To bring about this result it was necessary to use somewhat larger

TABLE IX

INFLUENCE OF BICHROMATE CLEANING FLUID UPON WASSERMANN REACTION WITH SYPHILITIC SERUM

DILUTION OF BICHROMATE SOL. C.C.	INFLUENCE UPON			
	WASS. REACT.*	ANTIGEN CONTROL	SERUM CONTROL	HEMOLYTIC CONTROL
1:200	++++	+	++	++
1:300	++++	–	+	+
1:400	++++	–	–	–
1:600	++++	–	–	–
1:800	++++	–	–	–
1:1000	++++	–	–	–
1:2000	++++	–	–	–

*Conducted with an antigen of acetone-insoluble lipoids.

doses of the three substances than required of each to destroy the erythrocytes alone, indicating that the serum tended to protect the cells and that these acids and alkali produce hemolysis or falsely negative Wassermann reactions by a direct lytic effect upon the erythrocytes.

These experiments have shown quite conclusively that minute amounts of alkali and mineral acids are markedly antilytic probably by means of a destructive influence upon complement and if present in the test tubes or other glassware may yield falsely positive Wassermann reactions by reason of their supposedly anticomplementary properties; conversely larger amounts of both may prove hemolytic and thereby yield nonspecific or falsely negative Wassermann reactions. For these reasons all glassware used in complement-fixation work must be chemically clean even if not bacteriologically sterile, to avoid erroneous results. The importance of these statements from a practical viewpoint is substantiated by the results of the following experiment (results shown in Tables X and XI):

Test tubes prepared in the following methods were employed in titrations of serum hemolysin and Wassermann reactions with negative, weakly positive and strongly positive serums:

Lot 0: New and unwashed test tubes of ordinary glass.

Lot 1: New and non-sol test tubes were boiled in strong soapy water and rinsed once with tap water.

Lot 2: Used non-sol test tubes were boiled in strong soapy water and rinsed once with tap water.

Lot 3: Same as lot No. 2 except that the tubes were rinsed very thoroughly.

Lot 4: Used non-sol test tubes cleansed with bichromate fluid and rinsed carelessly with tap water.

Lot 5: Same as lot No. 4 except that rinsing with tap water was thorough.

Lot 6: Same as lot No. 4 except that 2 per cent hydrochloric acid was used with careless rinsing.

Lot 7: Same as lot No. 6 except that rinsing was thorough.

All tables of Lots 1-7 were then allowed to drain and dry at room temperature.

The results of using these test tubes for titrating the same anti-sheep hemolysin with the same complement serum in dose of 1 c.c. of 1:20 dilution and washed sheep cells in dose of 1 c.c. of 2.5 per cent suspension after water-bath incubation for an hour, are shown in Table XI and indicate that new unwashed test tubes (Lot 0) and used test tubes boiled in soapy water followed by insufficient rinsing (Lots 1 and 2) may contain traces of an antihemolytic substance very probably anticomplementary in nature; the tubes of lot 4 and 6 on the other hand were markedly antilytic due to the anticomple-

TABLE X

INFLUENCE OF METHOD OF WASHING TEST TUBES UPON SERUM HEMOLYSIS

HEMOLYSIN** 1:1000 C.C.	RESULTS							
	LOT 0	LOT 1	LOT 2	LOT 3	LOT 4	LOT 5	LOT 6	LOT 7
0.1	S.H.*	S.H.	S.H.	S.H.	N.H.	S.H.	S.H.	S.H.
0.2	S.H.	S.H.	M.H.	S.H.	S.H.	S.H.	S.H.	M.H.
0.3	S.H.	M.H.	M.H.	M.H.	M.H.	M.H.	M.H.	M.H.
0.4	M.H.	M.H.	M.H.	C.H.	M.H.	C.H.	M.H.	C.H.
0.5	C.H.	C.H.	C.H.	C.H.	M.H.	C.H.	C.H.	C.H.

*N.H. = No hemolysis; S.H. = Slight hemolysis; M.H. = Marked hemolysis; C.H. = Complete hemolysis.

**Unit of hemolysin in proper test tubes was 0.4 c.c.

TABLE XI

INFLUENCE OF METHOD OF WASHING TEST TUBES UPON THE WASSERMANN REACTION

SERUMS	TRUE WASS. REACT.*	RESULTS							
		LOT 0	LOT 1	LOT 2	LOT 3	LOT 4	LOT 5	LOT 6	LOT 7
Normal	–	–	–	–	–	+	–	+	–
Latent syph.	+ +	+ +	+ +	+ +	+ +	+ + + +	+ +	+ + + +	+ +
Second syph.	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +

*Conducted with an antigen of cholesterinized alcoholic extract of heart muscle.

mentary activity of traces of hydrochloric acid and bichromate fluid after insufficient rinsing. None of the tubes of any lot contained sufficient of these substances to appreciably hemolyze 1 c.c. of the corpuscle suspension alone.

In the Wassermann reactions test tubes of Lots 4 and 6 proved antilytic (anticomplementary), yielding slight degrees of inhibition of hemolysis or falsely positive reactions (Table XI) with the negative or normal serum and increasing the degree of inhibition of hemolysis with the weakly positive syphilitic serum.

While these experiments were conducted with test tubes only, it is to be expected that the use of flasks, measuring cylinders and even of pipets (especially those of large calibre as 5 *c.c. and* 10 *c.c. capacity) may carry over sufficient acid or alkali to exert some antilytic influence, unless carefully and thoroughly rinsed with plain water if previously immersed in strongly acid or alkaline solutions.*

Kinds of Test Tubes and Other Glassware for the Wassermann Reaction.—The size of the test tube depends upon the total volume of fluid in the technic employed; it is advisable to use a tube of such width that the height of the column of the contents is not too great as this factor alone introduces an error in the work by interference with hemolysis. In an experiment (see Table XII) an antisheep hemolysin was titrated with 1 c.c. of 1:20 complement and 1 c.c. of a 2.5 per cent suspension of sheep cells, in test tubes of two sizes; the correct unit of this hemolysin was 0.4 c.c. of 1:2000 dilution whereas in a narrow tube (diameter 6 mm.) hemolysis was incomplete in this amount and particularly when the total volume was brought up to 5 c.c. with saline solution. Further reference to the influence of volume upon serum hemolysis and the Wassermann reaction will be made later; at present we introduce this experiment to show the practical importance of using test tubes of such diameter that the total volume will not be of a greater depth than 5 cm. in order to avoid a possibility of error. Furthermore, the diameter should be such that the contents may be thoroughly but gently mixed by rocking the tube instead of requiring capping with a finger and reversing several times.

In the methods which we are proposing as a standard technic, the test tubes are of rounded bottoms, with no lip and measure 8.5 cm. in length with an internal diameter of 12 millimeters (the walls are about one millimeter in thickness, which wear well).

Table XII

The Retarding Influence of a Narrow Test Tube with a Large Volume of Fluid upon Hemolysis*

SIZE OF TEST TUBE	COMPLEMENT 1:20 C.C.	SHEEP CELLS 2½% C.C.	TOTAL VOLUME C.C.	HEMOLYSIN 1:2000					
				0.1 C.C.	0.2 C.C.	0.3 C.C.	0.4 C.C.	0.5 C.C.	0.6 C.C.
100x 6 mm.	1	1	2.6	S.H.	S.H.	M.H.	H.	H.	H.
100x 6 mm.	1	1	5.0	S.H.	S.H.	S.H.	M.H.	M.H.	M.H.
120x16 mm.	1	1	2.6	S.H.	S.H.	M.H.	H.	H.	H.
120x16 mm.	1	1	5.0	S.H.	M.H.	H.	H.	H.	H.

*Water-bath incubation for one hour.

It is highly desirable to avoid tubes made of very thin glass (as used in chemical work for boiling) or of glass which is too thick; the former break too easily in washing and the latter are apt to crack during sterilization. These tubes are also sufficiently wide to permit easy cleaning with a brush, if necessary.

For mixing large volumes, as in the preparation of corpuscle suspension or dilutions of complement serum, we advise the use of volumetric flasks rather than the ordinary graduated cylinders because of greater accuracy. The glass-stoppered graduated cylinders (50 to 100 c.c. capacity) are more convenient, however, for measuring intermediate amounts, and may be used if carefully selected on the basis of accuracy in graduations. For measuring any amount of fluid under 50 c.c. we believe it is better to use an accurate 10 c.c. pipet and reserve the graduated cylinders or flasks for measuring larger volumes.

Method of Preparing Test Tubes and Flasks for the Wassermann Reaction.—

1. Since the material in the Wassermann reaction is noninfectious* it is unnecessary to sterilize the tubes and flasks by boiling after use as part of the cleansing process; furthermore, as a result of boiling the glassware repeatedly in soapy water (alkali), the glass becomes cloudy and unsightly. *It is highly desirable to use test tubes of uniform size which are physically and chemically clean, bright and glistening and preferably sterile; also to have this glassware set aside for use in the Wassermann reaction only instead of for general laboratory work.*

2. After use the tubes are emptied; rinsed in running tap water;

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*The only possible source of infection is spirochetes in cerebrospinal fluid and particularly from paretics; also in serum before inactivation. The danger, however, is remote; we have never heard of a laboratory infection by reason of work in the Wassermann reaction.

washed inside and outside in a pan or bucket of warm soapy water; thoroughly rinsed in running tap water and placed upside down in metal baskets and heated in a hot-air oven until a piece of fresh cotton placed in the oven has turned a light brown color. It is unnecessary to plug each tube with cotton, although it is advisable to plug the flasks because of their use during subsequent work; in this connection mention may be made of the report of Langer[5] who found that cotton may contain antilytic substances and to warn against permitting blood, complement serum or other reagents to soak into cotton stoppers by reason of the possibility of thereby dissolving out anticomplementary material. In some laboratories it is customary to boil the tubes in soapy water; rinse in tap water; immerse briefly in 1 per cent hydrochloric acid to neutralize the alkali of the soap; rinse thoroughly and sterilize. We believe the boiling and immersion in acid are unnecessary as routine procedures, although it is occasionally necessary to do this with tubes which are spotted and particularly dirty; *the rinsing after immersion in the acid bath must be particularly thorough in order to remove all traces of acid.*

3. New test tubes should not be used until thoroughly washed with soapy water, rinsed and sterilized as described above. In some laboratories it is customary to give them an acid bath as described.

4. While it is preferable to prepare the glassware on the day preceding the tests, the tubes are fit for use any time within a period of several days after preparation.

(B) *Possible Source of Error in Using the Same Pipet for Measuring Serums in the Wassermann Test.* In some laboratories it is customary to measure all serums with one pipet, the worker washing out the pipet one or more times by drawing in and expelling physiologic saline solution between serums; this would appear to be a source of error and particularly after pipetting a syphilitic and strongly Wassermann positive serum unless the washing were quite thorough. If serum is drawn up almost to the mouth end and particularly if it touches the cotton of a plugged pipet, the chances of carrying over sufficient serum to produce an error are particularly likely; a further objection in using the same pipet for all serums is the unavoidable dilution of serum with the washing fluid adhering to the interior of the pipet, rendering accurate dosage impossible even though the pipet is washed one or more times with the serum before it is measured out (and particularly if the bulk of serum is 1 c.c. or less). For these reasons it is undoubtedly better practice to have a separate pipet for each serum to be tested.

In Table XIII are shown the results of three experiments in which 1 c.c. pipets were previously used in syphilitic serum drawn to 0 and then used for pipetting a known normal or negative serum without washing and after washing one to three times in physiologic saline solution. In all instances the use of the unwashed pipet carried over sufficient positive serum to produce weakly positive reactions with the negative serum; after one washing in which the saline had been drawn to the same previous level of the positive serum, traces of serum remained in the pipet. After two or more washings the reactions were unchanged and apparently the pipets were clean although it is highly probable that minute traces of serum still remained, as can be surmised by the simple experiment of drawing normal sodium hydrate into a pipet and testing with phenolphthalein after repeated washings with water.

TABLE XIII

INFLUENCE ON THE WASSERMANN REACTION CONDUCTED WITH A NORMAL SERUM MEASURED WITH PIPETS PREVIOUSLY USED WITH POSITIVE SERUM AND CLEANSED IN VARIOUS WAYS

PIPETS	RESULTS		
	AFTER A ++++ SERUM	AFTER A ++++ SERUM	AFTER A ++ SERUM
Unwashed after using positive serum	++*	+	±
Washed once after using positive serum	±	±	−
Washed twice after using positive serum	−	−	−
Washed thrice after using positive serum	−	−	−
Washed in tap water and sterilized	−	−	−

*− = Negative; ± = Very weakly positive; + = Weakly positive (25 per cent inhibition of hemolysis); ++ Moderately positive (50 per cent inhibition of hemolysis). Tests conducted with a cholesterinized alcoholic extract of heart as antigen. The Wassermann reaction conducted with the normal serum was negative; all controls were satisfactory.

Kinds of Pipets for the Wassermann Reaction.—

1. As previously stated a sufficient number of 1 c.c. pipets should be provided and kept aside for the Wassermann reaction permitting a separate pipet for each serum.

2. The 1 c.c. pipets should be accurately divided into 0.1 cubic centimeters at least; it is not advisable to measure 0.01 cubic centimeter with them even though they are so graduated. The graduations should not extend to the tip (should stop about 2 cm. above)

because tips are so easily and frequently clipped that accurate measurement of the last 0.1 c.c. serum becomes impossible; from 8 to 10 cm. should be allowed from the tip of the mouth end to the first graduation line (0) to permit grasping.

3. The best pipets are long and slender rather than short and of thick glass; a pipet measuring 30 centimeters in its entire length (with the graduations from 0 to 1.0 c.c. measuring a total length of about 22 cm.) and with a diameter of about 4 to 5 millimeters, is best adapted for serologic work.

4. For measuring amounts less than 0.1 c.c. it is advisable to employ the special pipets having total capacity of 0.2 c.c. and divided into 0.01 c.c.

5. For measuring amounts of 1.0 c.c. or more as saline solution, corpuscle suspension, etc., accurately graduated 5-or-10-c.c. pipets may be used; it is not advisable, however, to attempt measuring 0.1 cubic centimeter with one of these large pipets, but to reserve them for measuring larger amounts as 0.5 to 1.0 c.c. or more.

Method of Preparing Pipets for the Wassermann Reaction.—

1. The first essentials for all pipets used in the Wassermann reaction are that they should be *chemically clean* and *dry;* it does not appear necessary that they should be sterile, although this is advisable. As previously stated, *it is highly desirable to have a complete set of pipets kept separate and aside for Wassermann work only* instead of for general laboratory work.

2. New pipets should be thoroughly washed and dried before use in order to remove any traces of anticomplementary or lytic substances which may be present.

3. After use *pipets should be placed without delay* in a large cylinder filled with water or physiologic saline with or without formalin to 1 per cent, in order to prevent serum or cells drying within the lumen of the pipet; a wad of absorbent cotton in the bottom will prevent clipping of tips of pipets as they are dropped into the jar with more or less force.

4. Before using again the pipets are to be thoroughly washed (inside and outside) under running tap water, drained, placed in metal cylinders or wrapped in paper and sterilized in a hot-air oven. It is unnecessary to plug the mouth ends with cotton, although this is optional with the individual worker and is advisable for the less experienced in the *art* of skillful pipetting.

5. When pipets become discolored from frequent use and especially by reason of sterilization without sufficient preliminary cleaning whereby serum becomes baked on the glass, they may be cleaned by complete immersion in 2 per cent hydrochloric acid or bichromate cleansing fluid overnight or for twenty-four hours, followed by washing in running water for two hours in order to remove all traces of acid before draining and sterilization.

(C) *Different Methods of Preparing Physiologic Saline Solution as a Possible Source of Error in the Wassermann Reaction.*—The saline solution commonly employed in the Wassermann reaction is prepared of sodium chloride in water in strengths varying from 0.7 to 0.9 per cent; with fresh erythrocytes 0.7 per cent is sufficiently isotonic but in our experience a 0.9 per cent is a greater safeguard against the breaking up of red blood cells. We have used throughout this study and can strongly advocate for routine work an 0.85 per cent solution prepared in large amounts by dissolving 8.5 grams of sodium chloride in 1000 c.c. of distilled water and sterilizing in an Arnold.

The kind of water employed in the preparation of physiologic saline solution varies in different laboratories; some use ordinary tap water, others bottled spring water and others a freshly or remotely distilled water. In those localities where the amounts of mineral salts in the river, well or spring waters are at normal, it does not appear in our experiments to make much difference what kind of water is employed provided it is filtered and of such quality as to be potable; in certain localities as where limestone and other alkalies abound, sufficient of these various salts may be present in the water to produce erroneous results and particularly since Hektoen has shown that a variety of neutral salts may be anticomplementary in relatively small amounts. In these districts, it is advisable to distil the water at least once before using in the preparation of physiologic saline solution.

Different brands of sodium chloride are in common use; some laboratories use only a C. P. (chemically pure) preparation while others use the ordinary table salt to be purchased in grocery stores.

We have conducted a series of experiments with 0.85 per cent saline solutions prepared of ordinary table salt and chemically pure sodium chloride dissolved in the following waters: (1) once distilled tap water; (2) triply distilled tap water; (3) ordinary tap water of Philadelphia which is filtered Schuylkill River water and (4) a bottled spring water. The waters were distilled in the ordinary Stokes still; it does not appear to make any difference whether the boiler and condenser are of glass, copper, tin or iron provided they are clean and free of incrustations of organic and inorganic material.

All of these saline solutions were prepared and tested in chemically clean and sterilized nonsol and flint bottles and test tubes; each was used in the preparation of dilutions of the same mixed serums of guinea pigs for complement, in the dilution of hemolysin and in the preparation of 2.5 per cent suspension of washed sheep cells. All were tested for isotonicity and the presence of hemolytic substances by mixing varying amounts with the cells; tests for antilytic (anticomplementary) activity were carried out in a series of titrations employing the complement and cells in constant amounts and varying amounts of hemolysin. The results of several experiments, briefly summarized in Table XIV, have shown but minor differences easily within the range of experimental error. Common table salt* (free of

TABLE XIV

INFLUENCE OF VARIOUSLY PREPARED PHYSIOLOGIC SALINE SOLUTIONS UPON SERUM HEMOLYSIS

0:85 PER CENT SOLUTIONS:	HEMOLYTIC SYSTEM			TEST TUBES	
	1:20 COMPLEMENT	HEMOLYSIN 1:1000	2½% CELLS	NONSOL.	FLINT
C.P. sodium chloride; triple distil. H_2O	1 c.c.	½ unit	1 c.c.	S.I.H.*	S.I.H.
“ “ “ “ “ “	“	1 unit	“	C.H.	C.H.
C.P. sodium chloride; tap water	“	½ unit	“	S.I.H.	C.H.
“ “ “ “ “	“	1 unit	“	C.H.	C.H.
C.P. sodium chloride; once distilled	“	½ unit	“	S.I.H.	S.I.H.
“ “ “ “ “	“	1 unit	“	C.H.	C.H.
Common table salt; triple distilled	“	½ unit	“	S.I.H.	S.I.H.
“ “ “ “ “	“	1 unit	“	C.H.	C.H.
Common table salt; tap water	“	½ unit	“	S.I.H.	M.I.H.
“ “ “ “ “	“	1 unit	“	C.H.	C.H.
Common table salt; once distilled	“	½ unit	“	S.I.H.	S.I.H.
“ “ “ “ “	“	1 unit	“	C.H.	C.H.
C.P. sodium chloride; Purock water	“	½ unit	“	S.I.H.	S.I.H.
“ “ “ “ “	“	1 unit	“	C.H.	C.H.

*C.H. = Complete hemolysis; S.I.H. = Slight inhibition of hemolysis; M.I.H. = Marked inhibition of hemolysis.

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*In the experience of one of us (J. A. K.) a saline solution prepared of ordinary table salt was once found to be highly antilytic and on another occasion a solution prepared of a C.P. sodium chloride purchased of a reliable firm was found markedly hemolytic in 1 c.c. of 0.85 per cent. Unfortunately the salts were not analyzed, but repeated tests to check the quantities of salt and water were made with identical results indicating that the error was in the salt.

lumps) appeared to be as good as chemically pure sodium chloride; ordinary tap water (potable) was as good as triply distilled water. Regardless of these results we believe it is *advisable to use C. P. sodium chloride and a freshly distilled water;* very probably a fresh tap water is preferable to a stale distilled water.

Additional experiments with sterile and nonsterile 0.85 per cent saline solutions freshly prepared of the same salt in the same water, showed no differences in their properties for hemolytic work. Experiments with portions of the same water with and without previous boiling to drive off carbon dioxide, showed no differences and it would appear unnecessary to boil the water for this purpose although we believe that *freshly distilled water* is best in the final analysis for the preparation of the saline solution.

Method of Preparing Physiologic Saline Solution for the Wassermann Reaction.—

1. Keep C. P. sodium chloride in a tightly stoppered bottle; if sufficient moisture has collected to render the salt somewhat lumpy dry a portion in the hot-air oven for ten or fifteen minutes before weighing.
2. Weigh out 8.5 grams and dissolve in 1000 c.c. of freshly distilled water in a chemically clean and dry flask furnished with a gauze-covered cotton stopper; filter through a good paper.
3. Sterilize by heating in an Arnold for an hour; smaller bulks require less heating. (Do not sterilize in an autoclave in order to avoid possible concentration of salt by loss of water in steam.)
4. Before using in the Wassermann reaction it is well to test the toxicity by adding a drop of washed blood cells to 5 c.c. of the solution in a test tube; if there are no immediate signs of lysis or none after gentle mixing and standing aside for half to an hour, the solutions may be accepted.

SUMMARY

1. It is highly important to have all glassware used in the Wassermann reaction (pipets, test tubes and flasks), chemically clean and free of all traces of acid or alkali by reason of the marked antilytic (anticomplementary) and hemolytic properties of these substances.
2. Amounts of sodium hydroxide as low as 1 c.c. of a 1:400 dilution of a N/1 solution in 2 to 3 c.c. of fluid may be anticomplementary while 1 c.c. of a 1:100 dilution proves hemolytic; approximately 1 c.c. of a 1:500 dilution of N/1 solution of hydrochloric acid is anticomple-

mentary and 1 c.c. of a 1:300 dilution hemolytic. Bichromate cleaning fluid proved anti-complementary in amounts as low as 1 c.c. of a 1:900 dilution and hemolytic in 1 c.c. of a 1:600 dilution. *It is possible that minute traces of acid or alkali in the glassware may be responsible for falsely positive Wassermann reactions with normal serums;* large amounts may produce negative Wassermann reactions with syphilitic serums, probably by reason of the direct hemolytic activity of mineral acids and alkalies in amounts greater than sufficient to destroy complement.

3. The use of one pipet for measuring different serums in conducting the Wassermann reaction introduces the possibility of carrying over sufficient syphilitic serum into a normal serum to produce an erroneous result, unless the pipet is carefully washed between each serum. The use of a separate pipet for each serum is advisable.

4. Test tubes must be of a size suitable to the technic in order to avoid too high column of fluid in a narrow test tube, which tends to interfere with hemolysis.

5. Physiologic saline solution for the Wassermann reaction should be prepared of chemically pure sodium chloride in freshly distilled water in 0.7 to 0.9 per cent; preferably 0.85 per cent.

6. The kinds of test tubes and pipets advised for a standardized Wassermann technic and methods for cleaning and preparing them, are described.

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FREQUENT BUT NEGLECTED EVIDENCES OF SYPHILIS FROM THE SIDE OF THE NOSE, ACCESSORY SINUSES, AND EAR*

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It is interesting to note the various attempts at estimating the gross number of luetic cases in society. Estimates in various children's hospitals in England and America gave from 3 to 4 per cent of lues. In recent examinations for the army, before the war, a percentage of 40 was said to be luetic. The report (unpublished) of the Social Commission of Oakland, California, gave 100 per cent among prostitutes after three months of service. It is apparent that these figures do not represent to any appreciable percentage the prevalence of lues in the normal population.

A much larger percentage of children entering a hospital will be luetic than is found in a baby show or kindergarten. The men entering the regular army before the war were mostly single men between the ages of 20 and 35 and belonged to the class where the incidence of lues is large. As physicians we are prone to see a far higher percentage of the disease than actually exists, for it is the weakling, the ill nourished, the individual with obscure symptoms, that is most apt to fall into our hands, and a larger proportion of these are apt to be luetic than in ordinary life.

The examination of a body of students entering a university shows a very small proportion who give any signs whatsoever of lues, and if we estimate how large a proportion of the population grows up without ever seeing a doctor, we begin to get a better outlook on life than when we view it from the inside of a clinic or hospital. I doubt if there is ½ of 1 per cent of the population which has been inoculated with this dread disease.

It is a mooted point as to whether an individual can show signs of syphilis without the spirochete being present, but I am firmly convinced that there are individuals who are considered healthy

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(not syphilitic) who have symptoms which give readily to mercury and potassium iodide, whose parentage is suspicious and who may transmit to the offspring these or other symptoms which may be assigned to the inherited condition.

We know that lues may be transmitted to the fetus by a mother who has been infected before or after conception, the father being free of infection. Knowing that the spirochete may be small enough to be included within the spermatozoon, may we have a luetic child by a noninfected mother, infection taking place through the spermatozoan; and what influence is stamped upon a child born of a noninfected mother by a luetic father who carries no spirochetes in the sperm.

Syphilologists say there is no syphilis without the spirochete and none in the third generation, an assumption we can most fervently hope is the case, but there are certainly robust individuals exhibiting a negative Wassermann, showing signs which are very suggestive of those we see in luetic patients, and where there is no reasonable evidence of a personal infection in whom the symptoms give readily to antiluetic treatment. Until it has been positively proved that these are not due to a luetic infection, it is well for therapeutic purposes, to consider this possibility, as it sometimes saves the patient a great deal of unnecessary suffering or inconvenience.

Among these symptoms are a nerve deafness, shortened bone conduction, vestibular abnormalities, a tendency of the mucous membrane to a venous stasis and an oversecretion often accompanied by asthma. I have seen luetics in whom these symptoms have arisen after the infection and whole families with negative Wassermanns in whom these symptoms were present in various members of the family and who gave readily to mercury rubs. While we are waiting for further evidence, we are constrained to assume the old hypothesis that lues may generate a toxin which may be transmitted to the offspring without the spirochete. The only other hypothesis is that the spirochete is present but in an attenuated form.

The basic morphology of the pathology of syphilis is a deposit of small round cells due to the toxic influence of the spirochete, and most symptoms may be traced to this deposit. The later lesions, the ones actually made so much of in textbooks, are the result of this deposit in conjunction with mixed infections, and are as a rule easily diagnosed; they are the ulcerations and necroses due to the thrombosis of the veins on account of the pressure; they lead to our septal perforations and sequestrated bones which latter may be so extensive as to include the body of the sphenoid which was removed *in toto* in one of my cases. It is far less important to be able to diagnose these very apparent lesions than it is to locate the early disturbances due alone to the leucocytic deposit.

I am, therefore, not going to inject into this paper a description of these common well-known diagnostic features, but I want simply to call attention to a few symptoms which are often overlooked, or that need emphasizing. It has been said, and justly so, that any symptom may be the result of a syphilitic infection, so that it becomes incumbent upon the diagnostician to exclude this disease as a possible factor before proceeding further in any obscure case. There have been operations done on syphilitic cases, which cases would have yielded to KI and Hg.

We have found in many luetic individuals a tendency of the mucous membrane in general, or certain parts of them to assume a bluish tinge; the normal pink color bordering sometimes on a yellow, is lost in a thick dusky, bluish red; this is not the angry red of an acute inflammation as seen in a streptococcus throat or the more sluggish red seen in the larynx of a smoker, both of which are produced by the dilatation of the arterioles. This luetic mucous membrane looks exactly what it is, as though there was a deposit which was encroaching upon the veins, preventing the outflow of blood. Turbinates will be large, often filling the nasal cavity and the feeling of stuffiness will be the one symptom which will send the patient to the doctor. One does not confuse this with the stuffiness arising from vasomotor disturbances, as seen in asthma or hay fever; the appearance here is entirely different and easily recognized at a glance, with its ashy color. This bluish color and swelling may be confined to the nose alone or be recognized in the mouth, throat, larynx, and bronchi as well. On shrinking the nasal mucous membranes with cocaine and adrenaline the bluish tint does not disappear as in other affections and we are still able to move the thickened membrane on its underlying bone. If we inadvertently take the tonsils out of these patients, the fossæ do not heal as readily as usual, although the ultimate result may be entirely satisfactory. A larynx or throat exhibiting these characteristics is very susceptible to the influence of irritants. Tobacco and alcohol are not tolerated at all well. Instance, the frequent hacking cough of tabetics who are smokers. These all show the characteristic blueness of the larynx and the cough at once disappears on stopping the tobacco. I always say that lues and alcohol and tobacco can not travel together; they certainly are not good bedfellows.

The function of these mucous membranes is evidently markedly interfered with, as the patient frequently complains of an over-secretion from the nose and throat. They "catch frequent colds" and will often be laid up for three weeks at a time every four months or so "with a cold." One of my patients, a girl of eighteen, has lost much of her schooling on account of this infirmity and yet was in perfect health in every other respect, weighed 160 pounds and had never had a sign of congenital lues. There was a triple positive Wassermann and the nasal mucous membranes became normal and a tendency to an oversecretion disappeared promptly on exhibiting mercury inunctions. For the past two years she had been entirely free of "colds." These mucous membranes easily break down and if careful search is made, scars of old lesions will be found in the tonsils, pharynx, palate, and nose.

As some patients show only a tendency to "catching cold" in the nose with a slight secretion, others will have an enormous quantity of a ropy discharge which may actually be pulled out of the antrum. In one case this occurred on one side, subsided and then appeared on the other side, eventually involving all the sinuses. Not knowing what I had, I opened all, only later to find a positive Wassermann and relief through mercury rubs. In this particular case the nasal secretion is as a rule accompanied by a thick secretion from the bronchi and the patient has been repeatedly treated for tuberculosis, but makes a prompt recovery on exhibition of mercury; never has the tubercle bacillus been discovered in the sputum. At one time for a period of a year, there was an exaggerated asthma which was controlled by rubs only.

The sinuses therefore do not escape, the same pathology appears here as in the nose and the x-rays show that the infiltration may extend to and involve the periosteum. This gives us another good diagnostic feature, as a cloudy sinus or antrum without any pus should make us suspicious of lues. One of my cases puzzled me for sometime on account of this clouding on the whole left side, frontals, ethmoids, and antrum, and was only made clear by making a diagnosis of lues and proving it by a Wassermann. That the thickening of the mucous membranes is quite general in lues is evident by the pictures of the bronchi obtained by the roentgenologists who are quite familiar with the shadows cast in this locality. The involvement of the periosteum over the sinuses often gives us a very interesting picture both visual and through the x-ray. The outline of the frontal sinus may easily be seen on the forehead and may be palpated. These cases have no pus in the sinuses, are not tender, and cast a shadow on the x-ray plate which is characteristic of lues. The shadow of pus or serum is uniformly dense, and if the picture is taken with the head upright, a level line may be shown. In lues, on the other hand, the shadow is blotchy, a light area appears as frequently at the bottom as at the top, the shadow is not confined to the sinus area but passes out into the surrounding skull. These cases come complaining of a general headache and all symptoms readily disappear on prescribing mercury rubs. All inflammatory processes in the sinuses have a tendency to give a periosteal thickening which will cast a shadow on the x-ray plate long after the inflammation has passed, and this fact should not be overlooked in making a diagnosis. This thickening as mentioned above is more evenly distributed than in lues.

The nerve lesions found about the nose are those of the olfactory, lack of ability to perceive odors, and of the fifth and vasomotor, the latter already noted. Pain in lues is as a rule referred to other parts of the head than the nose, as for instance, pain coming from the sphenoidal region will be noted in the ear or back of the head, and from the frontals to the top of the head; that due to enlarged turbinates is a heavy pain over the eyes. One seldom finds the pain referred to the inside of the nose itself.

Syphilis of the middle ear, like tuberculosis, is not as infrequent in occurrence as is generally believed, but is seldom diagnosed. So often have radical otologists said that an ear which had discharged for three months should be operated radically, that one is forced to believe that they overlooked the possibility of a syphilitic influence. Such a case was vividly forced to my attention by one of our prominent otologists entering on a tirade of abuse in a medical society meeting at the maltreatment undergone by a patient of mine, who had lost her hearing in one ear, according to him, and was losing it in the other because she had not been operated. The mucus discharge had been accentuated because the patient had neglected her rubs and was readily relieved by treatment. The middle ear lesion in this case is apparently the same as that of the nose, the picture of the mucous membrane reminding one very much of that seen in the nose.

The patient with middle ear syphilis comes complaining of a severe deafness and ringing in the ear, possibly with dizziness. If seen early, one thinks immediately of a severe acute infection without pain as seen in streptococcus mucosus infection, but the color of the drum is more that of a passive congestion. A paracentesis gives no secretion, but one is startled by the rapidity with which the drum melts away; in twenty-four hours nearly the whole drum may be gone. The mucous membrane is now seen to be thick, bluish red and a ropy mucoid secretion is with difficulty removed by persistent sponging. The patient may not know that the ear is discharging at all; if the nasal discharge is active, that from the ear will probably be also, and the patient will clean the ear with cotton, a couple of times a day. Unless there is added a purulent infection to mask the case, the ear remains in this condition indefinitely, there being alternately periods of entire dryness and slight secretion, which latter may be relieved by the exhibition of mercury. To what extent syphilis is responsible in the production of a bone necrosis in the middle ear and mastoid, I am not prepared to say; but I do know that I have operated a case showing a marked necrosis which would not heal after a year's futile effort at local treatment when a positive Wassermann was discovered and where the case gave promptly to mercury. Probably both a mixed infection and syphilis combined to produce the necrosis.

A diagnosis in these cases is helped out greatly by a study of the functions of the internal ear and eighth nerve.

For twenty years or more it has been pretty thoroughly recognized by otologists that the eighth nerve is particularly vulnerable to the toxins of syphilis and gradually there has been collected a valuable group of symptoms which are in the development; these are more constant than those of the eye which have been given so much prominence by the ophthalmologists.

Tinnitus, impairment of hearing, shortened bone conduction, vertigo disturbances of equilibrium, and impairment of the turning and caloric reactions have all been for years recognized as being present in syphilis but have been grossly neglected by the diagnostician whether otologist or internist. It is in the doubtful cases where the eye findings have been most valuable and it is here also that a thorough knowledge of the ear findings will be equally appreciated in the future.

The points to be observed and studied, then, in the diagnosis of syphilis of the labyrinth and eighth nerve are, from the side of the cochlea,

1. Shortened bone conduction.
2. Probable lateralization.
3. Rinné positive in the presence of impaired hearing.
4. Islands of hearing demonstrable.
5. Tinnitus.

From the side of the vestibule.

1. Progressive reduction of the nystagmus time (below 26 seconds) after turning, or reduction remaining constant in the presence of other evidence of syphilis.
2. Absence of a turning reaction with a caloric reaction present, or vice versa.
3. Irregularities in the reactions between the vertical and horizontal canals.
4. Vertigo present without nystagmus or exaggerated after turning, or caloric nystagmus without vertigo.

The probable cause of all the irregularities of function is a toxin attacking the nerve, and it has been suggested that the frequent rapidity of action and early onset may be influenced by the anatomic peculiarity of the nerve, it being without a neurilemma. This may help to account for the early shortening of the bone conduction which appears sometimes within 24 hours succeeding the primary infection.

Mackenzie has recently reviewed the literature of this subject, and has shown that there is an early deposit of spirochetes in the nerve itself and in the capsule of the labyrinth; the contents of the labyrinth is free of spirochetes. The presence of the spirochete implies an increase of the lymphocytes and hence the possibility that the neuritis may exist regardless of toxin.

There is nothing about the tinnitus or impaired hearing which in itself is characteristic of syphilis; in fact, all of the eighth nerve manifestations must be taken as a group and compared one with the other. The main characteristic in them all is the disharmony between them; the disproportion between the markedly shortened bone conduction and good air conduction; the intense tinnitus in some with good hearing; in others the marked dizziness and normal or lowered turning and caloric reaction, or vice versa, the exaggerated turning and caloric reactions and small amount of dizziness; marked vestibular impairment with small cochlear involvement; a prompt caloric with slow turning reaction, or vice versa, a prompt turning reaction with slow caloric; a slow caloric for the vertical canals, and prompt for the horizontal. Of course these disharmonies are characteristic of any neuritis of the eighth nerve, be it from the intestinal toxemias or from some intercranial pressure and have to be analyzed with this in mind. That they appear in other affections makes them none the less valuable than does the presence of a choked disc in more than one pathologic condition. A child of ten years who has become gradually deaf, over a period of years, with a reacting vestibular apparatus and with no dizziness or disturbance of equilibrium, probably has syphilis and not a brain tumor. A man with a history of an injury to the head, a rapid loss of hearing, and marked disturbances of the equilibrium, with active vestibular reactions, is more apt to be suffering from a tumor.

In explaining the presence of a caloric reaction without a turning reaction, in a case of lues, Neumann held that in all luetic nerve lesions, there was a loss of the adequate function of the nerve before an inadequate function is destroyed, in the case of the vestibular, the turning reaction would disappear before the caloric, the latter being an abnormal stimulus instead of a normal, but it has since been proved that this is not the case, that the converse may be present and therefore we are forced to the conclusion that there is a selective action on the part of syphilis for groups of fibers without the whole nerve being involved, and that any group may be picked out to the exclusion of any other.

The phylogenetic development of the various groups of fibers of the eighth nerve also has no bearing on the subject in hand as has been claimed, as the cochlear branch which is said to be the latest, is apparently no more often involved than is the vestibular.

The enthusiastic exploitation of one symptom or group has led to much confusion which will probably be avoided more and more in the future, as we get more light on the subject; instance, the shortened bone conduction. This is in reality a valuable symptom and does appear early but it is not generally recognized that it appears early in many cases of acute infections. Even head colds often show it markedly present, a case where we would naturally expect it to be lengthened. We get it also in cases of nerve exhaustion and in cases of intracranial pressure and brain tumor. In other words, it is present wherever there is a chance for a neuritis, either toxic or from pressure. It is a valuable symptom if interpreted properly.

Much stress has been placed on the absence of ability to perceive the high tones, as an evidence of syphilis, but I have found with Mackenzie, that cases vary as to the part of the scale involved. The lower tones are as often out as the high tones and frequently the whole tuning fork scale is well heard while the voice and the watch are poorly heard. It is these unlooked for results that have most often called my attention to the possible presence of syphilis. Jones pays particular attention to the time reduction of the nystagmus, equally interesting is the reduction in intensity of the nystagmic motions. Frequently I have thought on first turning the patient, that there was no nystagmus, but in a better light, observed a small movement over a considerable period of time. I have also noticed if the turning was repeated a number of times, the nystagmus became more intense, as though the degenerated nerve had been stimulated to better action.

I have never had opportunity to test out the ability of the syphilitic to recognize his position in space or his ability to recognize the direction in which the trunk is moving, functions of the saccule and utricle, but have no doubt that these functions will be found to be equally impaired, and possibly after the war some data may be obtained from those who have examined large numbers of aviators by means of the goniometer. It is to be hoped that records have been kept in cases of lues.

NEUROSYPHILIS OF THE PARETIC TYPE

Critical Examination of Doubtful Cases

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IN any hospital where cases are carefully studied and where there is a critical discussion concerning diagnoses at regular staff meetings, there is sure to be divergence of opinion in some cases. The various types of neurosyphilis are perhaps the best understood group of mental ailments, and the real margin of error in diagnosing them has been small during the past ten years. Southard[1] in 1910 and Orton[2] in 1913 reported 85 per cent accuracy. Darling[3] in 1918 reported 100 per cent accuracy. In January 1916,[4] attention was called to the necessity of close cooperation between laboratory workers and clinical staffs with special reference to the coordination of the findings of both before trying to differentiate between the various forms of neurosyphilis. At that time the opinions given at staff meetings concerning 697 routine admissions to the Warren State Hospital were studied, and 87 (12.5 per cent) were found to be of possible syphilitic origin. Of these 69 (9.9 per cent) were, in the opinion of the majority, unquestionable cases of general paralysis of the insane, and 5 (0.7 per cent) were vascular neurosyphilis. The remaining 13 cases (1.8 per cent) called forth discussion at the staff meetings because of symptomatology resembling both neurosyphilis and some other condition. Two years and a half have now passed and further observations have made possible a permanent, or at least semipermanent, classification of the cases in this latter group. The problems presented by these atypical cases are demonstrated in the following abstracts of the case histories.

CASES FINALLY CLASSED AS NEUROSYPHILIS OF THE PARETIC TYPE

Case No. 1.—(8136) Male, born 1881, married, skilled laborer, nativity Michigan, residence Pennsylvania. Father alcoholic. Early life normal. Father of three healthy children. Industrious and respected citizen. In 1910 slow change of disposition with gradual loss of ability at work began. During the latter part of 1912 he sat about home in a dull, stupid condition, failed to accomplish simple tasks, busied himself collecting rubbish, grew unstable emotionally, was forgetful and generally childish. During this period he had many epileptiform convulsions, projectile vomiting and severe headaches. When admitted, February 4, 1913, he was deeply demented and required constant nursing care. The mental characteristics recorded at that time include paucity of thought and speech, defective memory for both recent and past events, very low grade intelligence, clouded consciousness, slowness of apprehension, blunted attention, expansive delusions, lack of insight and mild euphoria. Physical examination showed spastic gait, fine tremors of tongue and hands, slurring speech, Argyll Robertson pupils, hyperactive knee reflexes, spurious right ankle clonus, tremulous, untidy writing and washed out expression. No optic atrophy or choked disk. Acquired syphilis about 1903. Laboratory reported Wassermann reaction in the blood and spinal fluid positive, globulin increased, cells 5 per c.mm. Eleven other specimens of the spinal fluid were examined and all showed similar evidences of syphilis. During a year of hospital residence patient passed through a quite typical course of paresis, finally dying with paralysis of deglutition and the bladder. Permission for necropsy refused.

CASE NO. 2.—(8479) Male, born 1876, married, machinist, nativity and residence Pennsylvania. Maternal grandfather and one brother tuberculous; father apoplectic. Early life normal. Worked steadily at his trade during adult life. Habits excellent. About January, 1913, he began to grow inefficient at his work and a little later defects of speech, memory, and judgment developed. January 11-13, 1914, he had a series of convulsions. When admitted, January 16, 1914, he was confused, disoriented, noisy, incoherent and resistive. After a few days he became more quiet and the records describe garrulous conversation, faulty memory, ridiculous errors in simple mathematics, partial clouding of consciousness, slowness of apprehension, blunting of attention, poor judgment, changeable emotions and a few persecutory delusions. Physical examination showed sluggish, unequal pupils, spastic gait, fine tremors of hands and tongue, hyperactive knee reflexes, double Babinski, tremulous, untidy writing, relaxed facial muscles and slurring speech. The laboratory reported Wassermann reaction positive in the blood and spinal fluid, globulin increased, cells 0. History from the family physician of syphilitic infection in 1911. Four Swift-Ellis treatments were followed by distinct mental improvement, and he remained in a comfortable condition until May, 1915, when a series of convulsions was followed by death. The treatment given had no effect on the Wassermann reaction in either the blood or the spinal fluid. Permission for necropsy refused.

CASE NO. 3.—(8303) Male, born 1838, widower, furniture dealer, nativity Bavaria, residence Pennsylvania. Father apoplectic; sister had chronic heart disease. Common school education. Advanced from a cabinet maker to owner of store and retired in 1899 because of a nervous breakdown, but with enough money to keep himself in comfort. During the six years preceding commitment, he had numerous apoplectiform attacks, none of which left any residual paralysis. In June, 1912, had a short period of amnesia. In December, 1912, he became apprehensive, "lost his memory," and consciousness became more or less clouded. At the time of admission, July 23, 1913, the records describe poorly retained elementary knowledge, incapacity in simple mathematics, clouded consciousness, dull apprehension, blunted attention, gross faults of memory, confabulation, defective judgment, delusions of poverty, and euphoria. Physical examination showed blood pressure of 125 mm., slight systemic arteriosclerosis, enlarged heart, myocardial weakness, fine tremors of hands and tongue, sluggish pupillary reaction to light, overactive knee reflexes, tremulous, untidy writing, mild ataxia, clumsiness, poor vision and drawling speech. Laboratory reported blood picture of secondary anemia, Wassermann reaction positive in the blood and spinal fluid, globulin increased, cells 8 per c.mm. He improved and was able to wander about the grounds, but at his best would become confused and lost amid familiar surroundings. Emotional reactions were shallow and shifted frequently; judgment was very bad and he never gained any insight. In the fall of 1913 he became bedfast and death occurred March 25, 1914. The postmortem examination showed moderate cerebral sclerosis and typical paretic changes.

Case No 4.—(8253) Male, born 1851, married, laborer, nativity and residence Pennsylvania. Nothing known of heredity. Common school education. During adult life he worked on farms and in the woods, earning a precarious living until advancing years made him subject to charitable support. Was a periodical alcoholic throughout life. In 1912, failure of memory, garrulous, wandering conversation and defects of judgment began. When admitted, June 11, 1913, he was restless, deeply demented, distoriented and exceedingly incoherent. There was no intelligent response to question nor any conversation except a few tremulous, disconnected monosyllables. Physical examination showed extreme weakness, emaciation, systemic arteriosclerosis, aortic insufficiency, sluggish pupillary reaction to light, hyperactive knee reflexes, loss of vesical and rectal control, and anesthesia of the left leg. Laboratory reported persistent sugar in the urine. Wassermann reaction positive in the blood and spinal fluid, globulin increased, cells 12 per c.mm. Death occurred July 21, 1913. Autopsy showed typical paretic changes and a localized area of nonsyphilitic softening over the right ascending parietal convolution.

Case No. 5.—(8715) Male, born 1854, married, laborer, nativity Ireland, residence Pennsylvania. Nothing known about heredity. No educational advantages. Steadily employed at rough labor and gave his large family a good home. Some physical failure began as early as 1900. In 1912 complained of very severe headaches and a year later had to give up work. After that, emotional instability, irritability and delusions of infidelity developed. Some months later he had an apoplectic attack with right hemiplegia and disturbance of speech. When admitted, September 14, 1914, consciousness was clouded and conversation was unintelligible. Physical examination showed motor restlessness, general enfeeblement, systemic arteriosclerosis, blood pressure 150 mm., coarse tremors of hands, lips and tongue, relaxation of facial muscles, ataxia, tremulous, untidy writing, hyperactive knee reflexes, sluggish, unequal pupils, slurring, halting, unintelligible speech and no definite residuals of the reported hemiplegia. Wassermann reaction positive in the blood and spinal fluid, globulin increased, cells 60 per c.mm., colloidal gold curve 5555542100. As late as 1918 similar evidences of neurosyphilis have been reported by the laboratory. Since early in 1915 he has been a quiet, feeble patient, who sits about unoccupied but cares for most of his own wants. Only an occasional word of what he says can be understood, and he evidently can not read or write. He is irritable and emotionally unstable.

DISCUSSION

In Cases 1 and 2 the final diagnosis is based upon clinical and laboratory evidence, and since no autopsy was performed, can not be considered as absolutely proved. Nevertheless, the further progress of the disease, in both instances brought out the typical symptoms of general paralysis of the insane, and there can be little doubt concerning the diagnosis. In Case 1 there was a history of persistent, projectile vomiting associated with epileptiform attacks and severe headaches. This combination of symptoms made it necessary to consider cerebral gumma or tumor. As these symptoms were not observed at the hospital, and as the patient passed through the typical clinical stages of paresis in spite of energetic treatment, gumma and tumor seem fairly well ruled out. In Case 2 there was a definite history of mental symptoms developing within two years of the initial infection. This appears to have been the only reason for disputing the diagnosis of paresis, and because of it, three of the five physicians present when he was brought before the hospital staff are recorded as favoring vascular neurosyphilis. The symptoms here reported as developing later seem sufficient to make this favored primary diagnosis an unpopular second choice for final classification.

Case 3 illustrates a mental and physical breakdown in old age that closely approximates a simple dementia of sclerotic origin. The numerous apoplectiform attacks without residuals, the reflexes and the speech all draw attention to the possibility of paresis. The positive serologic tests proved a syphilitic element. The autopsy proved the presence of neurosyphilis of the paretic type, and also showed moderate cerebral sclerosis. It would be quite permissible to list this as a combined psychosis, but if we admit that syphilis is a very frequent cause of arteriosclerosis and that a certain degree of sclerosis is to be expected in a man seventy-five years old, it appears more rational to consider general paralysis to be the real cause of the symptoms recorded and of the patient's death. It is necessary to remember that in this case the cerebral sclerosis was only moderate and that there were no definite areas of softening.

Case 4 is similar to Case 3. In this instance the patient was thirteen years younger (sixty-two years of age). When admitted, dementia was so far advanced and restlessness so persistent that no really satisfactory examination could be made. There would probably have been little hesitation about diagnosing the condition a dementia of arteriosclerotic origin but for the positive Wassermann test. Because of the laboratory report, the case was called a combination of general paralysis of the insane and organic dementia of arteriosclerotic origin. The remarks concerning Case 3 apply in this instance, yet the prominence of the cerebral sclerosis and the definite, small, localized area of nonsyphilitic softening found at necropsy makes it necessary to recognize that there were two separate, yet closely allied causes for the mental and physical symptoms.

Case 5 is closely related to Cases 3 and 4. The unmistakable serologic evidence of neurosyphilis is combined with mental and physical symptoms quite compatible with general paralysis of the insane. These same mental and physical symptoms might, on the other hand, be accounted for by sclerotic brain changes. Because of their religious belief, the family refuse permission for necropsy; hence, there must always be some doubt as to the relative importance of the two probable causative factors.

CASES NOW LISTED AS TOXIC PSYCHOSES

Case No 6.—(8194) Male, born 1854, single, oil contractor, nativity and residence Pennsylvania. Father died of cancer; one brother committed suicide. Successful business man until 1908, when he became an invalid because of valvular heart disease. In February, 1913, he developed extravagant, grandiose ideas, became unduly irritable and exceedingly restless. When admitted, April 15, 1913, these characteristics persisted and in addition there was euphoria, clouding of consciousness, lack of judgment and unstable emotions. Physical examination showed poor nutrition, edema of dependent parts, pulmonary congestion, high blood pressure, systemic sclerosis, enlarged liver, ascites, incoordination, coarse tremors of tongue and hands, slurring speech, and defective pupillary reaction. Urinalysis indicated a chronic nephritis. History of syphilis in 1891, but Wassermann reaction was negative in both blood and fluid. Death occured May 3, 1913, and postmortem examination showed pial and cortical edema, chronic pachymeningitis, leptomeningitis and mild gliosis. No evidence of paretic destruction found. When first considered by the hospital staff, a diagnosis of toxic exhaustive psychosis was favored, but paresis was feared and a single Wassermann reaction was thought insufficient. In view of postmortem results, case must be finally classed as a toxic exhaustive condition dependent upon defective heart, kidneys, liver and blood vessels.

Case No. 7.—(8264) Male, born 1860, bigamist, teamster, nativity and residence Pennsylvania. Father alcoholic and mother apoplectic. Common school education. Worked steadily as a teamster and kept family in comfort. Used alcohol moderately throughout adult life. In 1909 diabetes developed and he was physically incapacitated thereafter. About April, 1913, a change of disposition began with irritability and general unreliability as prominent characteristics. Changeable emotions, grandiose ideas, loss of sense of values and ridiculously extravagant plans for the future were observed. A few weeks later, mild but very frequent convulsive attacks without sequelæ appeared. When admitted, June 14, 1913, consciousness was clouded, he was exceedingly incoherent, had no insight and showed great motor restlessness. Physical examination showed poor nutrition, myocardial weakness, speech defect, coarse tremors of tongue and hands, incoordination, disordered writing, normal pupils and normal reflexes. Repeated urinalyses showed specific gravity varying from 1.032 to 1.040, 0.1 per cent to 0.5 per cent sugar, positive acetone, and daily excretion of about 80 ounces. These findings were not changed by restricted diets. Owing to a series of unfortunate incidents, no Wassermann was done in this case. Death occurred in a convulsive attack July 19, 1913. The necropsy revealed interstitial changes in spleen, liver, kidneys, and heart. In the brain there was cortical atrophy and edema, diffuse gliosis and hyaline degeneration in the arteries, but no evidence of paretic destruction.

DISCUSSION

Case 6 represents a combination of mental symptoms frequently found associated with severe cardiovascular renal disease. In this particular case there was a definite history of syphilis and many of the mental peculiarities suggested paresis. Physically he showed incoordination, tremors, slurring speech and imperfect pupillary reaction to light, all of which are quite compatible with neurosyphilis. The single specimens of blood and spinal fluid obtained before death were negative to the Wassermann test. While totally negative serologic tests are very rare in general paralysis, such findings do occur, and syphilis ought not to be ruled out unless several examinations are made. In the discussion of this case, neurosyphilis of the paretic type and cardiovascular renal psychosis were considered, the latter being preferred. Autopsy proved the preference of the majority to be correct. When admitted, this patient was obviously in a dying condition and the question as to whether or not we are justified in making several spinal punctures, which only promise to definitely settle which of two fatal diseases is present, must always arise in such instances.

Case 7 exhibited mental symptoms that appeared to be very typical of paresis, and all physical signs except the reflexes and pupils indicated the same disease. The severe diabetes complicated the picture and at once raised a question concerning causation. The autopsy findings rule out neurosyphilis and remind us that diabetes mellitus can be complicated by mental changes closely resembling paretic neurosyphilis. Case 4 showed almost the same evidence of diabetes as Case 8, but in that instance the pupils and reflexes were abnormal and there was definite laboratory proof of neurosyphilis.

CASE LEFT UNCLASSIFIED

Case 8.—(8478) Male, born 1842, widower, miner, nativity Italy, residence Pennsylvania. No history available except commitment paper statement that he had been noisy and quarrelsome for a year. When admitted January 6, 1914, he was very feeble, completely disoriented, did not respond to questions, and apparently understood nothing of what went on. Physical examination showed numerous large, superficial scars, an eruption over entire back made up of slightly elevated, red papules arranged in distinctly semilunar formations, and some pits covered by black crusts about one-half inch in diameter; tortuous, hardened arteries; enlarged heart; muscle tremors; irregular and unequal pupils; hyperactive knee reflexes; left ankle clonus and Babinski and enlarged epitrochlear glands. Laboratory reported Wassermann reaction negative in the spinal fluid, globulin increased and no cells. No specimen of blood was obtained. Bronchopneumonia developed and caused death February 5, 1914. Permission for necropsy refused.

DISCUSSION

Case 8 presents little of value. He was a totally demented, dying patient with undoubted cardiorenal vascular disease of a very severe type when admitted. The eruption, enlarged epitrochlear glands, pupillary changes and knee reflexes raised the question of syphilis. One laboratory examination of the spinal fluid failed to show any serologic evidence of neurosyphilis. As autopsy permission was refused, the case has been left unclassified.

CASES NOW LISTED AS INCIPIENT PARESIS

Case 9.—(8103) Male, born 1883, single, carpenter, nativity and residence Pennsylvania. One brother, one uncle, and one third cousin insane. Early life normal. Selfish, introspective and ''peculiar'' personality. In 1911, broke wedding engagement without cause, worried over syphilitic infection, became ''changeable'' and ''moody'' in disposition, and stopped work because of general incapacity. Admitted December, 1912, and then showed some retardation, poor retention of school knowledge, imperfect orientation, omission of letters in writing, morose manner and vague, depressive ideas. Physically there were unequal knee reflexs, slightly irregular pupillary margins, moderately impaired pupillary reaction to light, a slight slurring of speech and very fine tremors of tongue and hands. Acquired syphilis in 1903. Laboratory reported Wassermann reaction in the blood negative, in the spinal fluid positive, globulin increased, cells 40 per c.mm. In March, 1913, he eloped and returned home. In 1918, he was reported to be working steadily and approximately normal mentally and physically.

CASE 10.—(8167) Male, born 1880, single, machinist, nativity and residence Pennsylvania. Father died of apoplexy. Early life normal and influences good. In 1900, began to drink and has since been incompetent in his trade because of this habit. During latter part of 1912 became very forgetful, irritable and suspicious. In March 1913, began to hear ''vague'' voices talking and complained unjustly of ''drink cure'' in his coffee. When admitted, March 21, 1913, he showed defects of attention, poor retention of school knowledge, inability to name months in rotation, etc. Physical examination showed sluggish pupillary reaction, fine tremors of hands and tongue, and normal knee reflexes. Laboratory reported Wassermann reaction in blood and fluid positive, cells 36 per c.mm. Syphilitic infection resolutely denied and treatment refused. Discharged June 13, 1913. Since then he has lived at home, done practically no work, drunk excessively and been ugly and irritable. No deterioration of mental faculites is recognized by the family.

DISCUSSION

Cases 9 and 10 have been classed as incipient paresis for lack of a better term. In both there were definite laboratory evidences of neurosyphilis combined with a few physical and mental symptoms of paresis. Neither had pronounced speech disorder, pupillary changes nor disturbance of reflexes, although there was slight abnormality of at least two of these functions in each. The mental changes were even less characteristic. Southard and Solomon[5] used the term ''paresis sine paresi'' to designate cases of laboratory neurosyphilis with no mental or physical changes that could be directly attributed to lues of the central nervous system. Cases 9 and 10 might be classed thus as one had a peculiar psychopathic make-up and the symptoms observed at the hospital were only an exaggeration of these natural characteristics while the other was committed because of excessive alcoholic indulgence which began during adolescence and could have caused all of the symptoms observed. In other words both of these patients were brought to the hospital because of episodes that could reasonably be expected to occur in nonsyphilitic individuals of their types and the discovery of neurosyphilis was merely an incident demonstrated during a thorough examination. The fact that they have returned to their homes and resumed the tenor of life along the same lines as before commitment here and had no further acute symptoms during a period of at least five years is enough to prove that the prognosis in such cases is a little different from that of ordinary paresis. Southard and Solomon do not venture to suggest what the future holds for a case of "paresis sine paresi" and the same uncertainty of prognosis exists in these cases. It is easy enough to say that the psychopathic personality of one and the confirmed alcoholism of the other will, in all probability, prevent them from leading truly useful lives; but whether or not the neurosyphilis will eventually cause pathognomonic symptoms and death is the important question that time alone can decide.

During the past few years several workers[6] have found positive laboratory evidences of syphilis in the spinal fluids of acute secondary syphilis, while others,[7] have reported as high as 20 to 60 per cent positive Wassermann reactions in the spinal fluids of late secondary and latent syphilis. It is quite certain that only a small percentage of these cases with early involvement of the cerebrospinal axis later develop paresis, vascular neurosyphilis, and allied conditions, yet it is very reasonable to suppose that members of this group are more liable to develop these serious conditions later on. Future serologic studies of the spinal fluid must be depended upon to establish the real relationship of secondary syphilis with involvement of the cerebrospinal axis, latent syphilis with positive spinal fluid serology, "paresis sine paresi," "incipient paresis," and true neurosyphilis.

CASES NOW LISTED AS DEMENTIA PRECOX

Case No. 11.—(8138) Female, born 1879, married, housewife, nativity and residence Pennsylvania. Nothing known about heredity. No education. Married a laboring man and cared for her home in a satisfactory manner. In 1911, during a pregnancy, she became apathetic, failed to care for her home, imagined that some one was going to injure her and had a few vagus auditory hallucinations. The mental symptoms subsided after delivery, and she resumed the care of her home. In January, 1913, she began to neglect her work again, failed to dress properly, and became afraid that some one was planning to carry her away. She was admitted to the hospital in February, 1913, and at that time was inactive, dull and apathetic. Conversation was very meager and her answers to questions indicated lack of mental activity. Orientation was imperfect, attention was blunted, memory was defective, and her powers of observation were abnormally limited. She complained that unknown people followed her and feared that she was going to be taken to some strange place, but would not elaborate these ideas, and talked about them without increased emotion. Once or twice she imagined she heard her child calling her. The physical examination showed unequal pupils, irregular pupillary margins, limited pupillary reaction to light, hyperactive knee reflexes and a slurring speech defect when trying to pronounce the test phrases. Laboratory reported Wassermann reaction positive in the blood and negative in the fluid, globulin negative, cells 4 per c.mm. During the past five years she has lived contentedly in a ward with demented patients and developed into a good ward worker. There has been but little change in her condition during this period except for a small gain in weight and a slowly increasing adaptability toward routine. At irregular intervals there have been short periods of irritability associated with impulsive tendencies. At present she has no pride in her personal appearance and is definitely apathetic. She does her routine work well but when this is completed she spends the remainder of the time sitting about unoccupied. Her conversation is desultory and strange use of words and phrases is frequent. There are numerous vaguely described delusions similar to those suggested in the following bit of her own conversation: ''The planet govern the country through me the only birth president. Everbody is a capitalist. There is just one person in each nation and one person in each state. That throws everybody in a different nation and a different nationality. That would throw new, poor people in the world.'' Definite hallucinations can not be demonstrated but they are suggested by statements such as, ''Through me the planets govern the world through telephone.'' She is poorly oriented, attention is blunted, apprehension is dulled, association processes are very meager, and she claims inability to recall much of her past life. Recently she has denied her marriage and the birth of her children. Laboratory now reports Wassermann reaction positive in the blood and negative in the spinal fluid, globulin negative, no cells, and colloidal gold 00000000000. The reflexes and speech continue to be slightly abnormal.

CASE 12.—(8759) Male, born 1879, single, clerk, nativity and residence Pennsylvania. Father, mother, paternal uncle, and sister had heart disease. Graduated from Princeton University and later from law school. In 1911 began to act suspicious of his associates, imagined he was being followed and developed a loose, persecutory delusion system. In 1913 he had a short period of unconsciousness followed by tremulous speech, desultory conversation, loss of ambition, foolish expenditures, irritability and inability to do his work. When admitted November 10, 1914, he outlined delusional interpretations of all events during the previous three years of his life and described distinct auditory hallucinations. Slurring speech, peculiar phraseology, looseness of thought, and apathy were observed. Physical examination showed irregular pupillary margins, quick pupillary response to light, hyperactive knee reflexes, tremors of the lips and tongue, ''washed out'' expression and ''shuffling'' gait. Acquired syphilis in 1904. In November, 1910, the Wassermann reaction was positive in the blood and negative in the spinal fluid, globulin was normal, there were no cells and the colloidal gold test showed no evidence of syphilis. In Febuary, 1914, Wassermannn reaction was positive in the blood and spinal fiuid, globulin was increased and there were no cells. For some unknown reason the colloidal gold test was not done at this time. In March, 1914, the blood Wassermann reaction was positive and all tests of the spinal fluid negative. Three Swift-Ellis treatments were given between March 20 and May 12, 1915.

Five specimens of the spinal fluid have been examined since this and none of these showed any evidence of syphilis. Three specimens of blood have all been positive to the Wassermann reaction in spite of energetic mercury treatment. Patient is still at the hospital and has settled down into a quiet dementia. At present there are vague disconnected, persecutory ideas, fragmentation of speech, neologisms, tremor of the lips, hyperactive knee reflexes, and irregular pupillary margins. Pupils respond to light quickly.

DISCUSSION

Case 12 appears to illustrate an instance in which positive serologic findings tended to cloud the vision of the examiner, as there is now almost no suggestion of paresis in this patient. The tremor of the lips is under excellent control and is, without doubt, a mannerism. The slight irregularity of the pupillary margins can be explained by an iritis of rheumatic or syphilitic origin, and slightly overactive knee reflexes are not definitely pathologic. The history of a short period of unconsciousness was considered another point in favor of paresis, yet similar disturbances are far from infrequent in dementia precox and as he has lived five years without a repetition of the episode, it seems more and more improbable that it was a paretic convulsion. In this particular case I am inclined to doubt the reliability of the single positive Wassermann in the spinal fluid because this evidence of neurosyphilis disappeared before the Swift-Ellis treatments were started, and has not returned since or, it may be that this positive reaction was caused by a small amount of blood contaminating the spinal fluid. This theory is tenable because it also explains why no colloidal gold test was made. On the other hand several observers have reported a large percentage of positive Wassermann reactions in the spinal fluids of secondary, tertiary, and latent syphilis. As we do not yet know how persistent these evidences of neurosyphilis are, it may be that a transient positive reaction such as this can be explained by placing the case in one of these groups. In spite of the fact that all of this patient's present symptoms point to dementia precox, it will be necessary to observe him carefully as long as he lives for the persistent recurrence of positive blood Wassermann reactions show that systemic syphilis is still present and there is still a chance of neurosyphilis developing later on.

When Case 11 was brought before the hospital staff every one agreed that there was a certain amount of congenital defect with consequent faulty mental development and based the opinion upon her reputation in her home community and lack of education in spite of opportunity to attend school. There was no such agreement concerning the type of the psychosis that had finally made hospital care necessary. It was generally recognized that a single negative spinal fluid was not enough to rule out neurosyphilis where there were such suggestive signs of that disease as Wassermann positive blood, abnormal pupils, speech defect and definitely overactive knee reflexes, but no two agreed as to the degree of probability of the presence of paresis. The slowness of movement and speech with the mild apprehensiveness that simulated worry led some to think of an atypical phase of manic depressive insanity or, as one expressed himself, "an unclassified depression in an imbecile," but what at first appeared to be mild depression has turned out to be apathy; the worry now seems to have been apprehensiveness; and the retardation of speech now appears as a paucity of thought. The passage of five years, with no increase of paretic symptoms and spinal fluid that is still negative to the Wassermann and colloidal gold test, seems enough to rule out the presence of an active neurosyphilis. During the same period of time continuous observation has failed to reveal the psychomotor retardation, depression, and worry that would justify a diagnosis of manic depressive insanity. There has been lack of affect, desultory conversation, fragmentation of thought, use of neologisms, imperfect orientation and a gradual retirement into a "dream world" with a consequent denial of family ties and former life interests. The case is now listed as congenital mental defect plus a deteriorative condition of the dementia precox type. This patient apparently has about the same chance of developing neurosyphilis later on as Case 12.

CASE NOW LISTED AS ALCOHOLIC DELUSIONAL INSANITY

CASE 13.—(8364) Male, born 1880, married, machinist, nativity and residence Pennsylvania. Paternal grandfather, father, five paternal uncles, and one brother alcoholics. Early life normal. Wandering type of skilled worker.

Father of one healthy child. Drank excessively since nineteen years of age. Contracted syphilis in 1911 and received immediate salvarsan treatment. Six months later secondaries developed. Treatment required stopping alcohol and shortly afterwards hallucinations appeared; first, terrifying visual; second, taunting derisive auditory and third more pleasant encouraging auditory. Faint calling of his name, occasional derogatory remarks and infrequent accusations persisted at intervals. Increased intemperance during 1912 was followed by more prominent mental symptoms and the development of vague delusions of persecution and infidelity. When admitted, September 23, 1913, the previously mentioned symptoms were present and he also showed intellectual and moral obtuseness, expansive ideas, and generally defective judgment. Physical examination revealed slurring speech, sluggish pupils, diminished patella reflexes and fine tremors of the lips, tongue, and hands. The laboratory reported Wassermann reaction positive in the blood and negative in the spinal fluid, globulin negative and cells 1 per c.mm. Two weeks later another specimen of the spinal fluid was tested and found positive to the Wassermann test but otherwise negative. During the past four years he has become institutionalized and is now a quiet, apparently contented, hospital resident. There are still vagus auditory hallucinations of a persecutory type that cause occasional short periods of resentment and irritability. He is very reticent about his troubles, but talks freely on other subjects. So far as can be learned no explanatory delusions have developed. He is neat, intelligently industrious, perfectly oriented, interested in current events, and has a good memory. His general physical health has been excellent except for periodic headaches and recurrent attacks of iritis which have been relieved by energetic treatment with mercury and iodides. At present there is slight impairment of pupillary reaction to light, some irregularity of pupillary margins and a very mild speech defect. The knee reflexes are sluggish. There is no tremor, no relaxation of the facial muscles, no loss of dexterity, no defect of writing and no ataxia. In May, 1918, Wassermann reaction was negative in the blood and spinal fluid, globulin negative and colloidal gold 01110000000.

DISCUSSION

Case 13 has an onset that is very typical of an alcoholic delusional insanity, and the present mental state is well explained by that diagnosis. The points brought out in the discussion that pointed to paresis were the undoubted presence of syphilis, expansive ideas, moral obtuseness, slurring speech, tremors, impaired pupillary reaction and diminished knee reflexes. Alcoholism readily accounts for a thickness of speech, tremors, low morals, and reflex changes. The iritis since admission and his statement that he had similar trouble before commitment accounts for the pupillary changes. The single positive Wassermann reaction in the spinal fluid can not be explained. The various possibilities are mentioned in the discussion of Case 12. Needless to say the future of this case is uncertain and careful observation is indicated as more typical symptoms of neurosyphilis may appear later on.

The opinions expressed when these patients were brought before the hospital staff for discussion of diagnosis are indicated by the accompanying table. It is impossible to tabulate all of the doubts and

CASE NUMBER	1	2	3	4	5	6	7	8	9	10	11	12	13
SPEECH DISORDERS	x	x	x	x	x	x	x		x			x	x
PUPILLARY CHANGES	x	x	x	x	x	x		x	x	x	x		x
REFLEX CHANGES	x	x	x	x	x	x		x	x		x	x	x
SEIZURES	x	x	x		x		x						
Early headache	x				x								
Visual disorder			x										
Hypalgesia	x	x	x	x	x	x	x	x				x	
Ataxia	x	x	x		x								
Nasolabial flattening	x	x	x		x								
Vocal change	x				x								
Writing disorder	x	x	x		x	x	x		x				
Loss of manual dexterity	x	x	x	x	x	x	x	x					
Paralysis	x		x	x	x								
Amnesia recent	x	x	x	x	x	x	x			x			
Quick shifting emotions	x	x	x		x	x	x		x				
Character change	x	x	x	x	x		x				x	x	x
Conduct slump	x	x	x	x	x	x	x	x	x	x	x	x	x
Intake impaired	x	x	x	x	x		x	x	x			x	
Consciousness clouded	x	x	x	x	x	x	x	x	x				
Fatigability increased	x	x				x	x						
Hallucinosis, rare										x		x	x
Chronology & storage poor	x	x	x	x	x	x	x	x		x			
Fabulation			x			x							
Oversuggestibility						x	x						
Judgment impaired	x	x	x	x	x	x	x	x	x	x	x	x	x
Fantastic delusions	x	x			x	x	x						
Insight absent	x	x	x	x	x	x	x	x	x	x	x	x	x
Early irritability			x		x	x	x	x	x	x		x	x
Wassermann reaction, blood	+	+	+	+	+	–			–	+	+	+	+
Wassermann reaction, fluid	+	+	+	+	+	–		–	+	+	–	–	–
Globulin	+	+	+	+	+			+	+		–	–	–
Cells per c. mm.	5	0	8	12	60			0	40	36	0	0	1
Colloidal gold test					+						–	–	–

x = Symptom indicated was present.

+ = Reaction positive for syphilis. Colloidal gold curve of the paretic type.

– = Reaction negative for syphilis. Colloidal gold curve not of the paretic or syphilitic type.

Where blanks are left evidence of the symptoms could not be elicited by questioning the family, and the symptoms were not observed at the hospital either because of their absence or because the patient's condition during hospital residence precluded determination of them.

Where blanks are left in the table of reactions no tests were made.

The so-called cardinal symptoms of paresis are indicated by capital letters.

opinions recorded in the staff meeting record book but most of them are pointed out.

A tabulation of the paretic symptoms observed in the study of these cases has been attempted and is here presented. While compiling this, much difficulty was encountered through varying types of nomenclature used by different physicians. Because of this there are a few symptoms checked in the table as present that are not definitely mentioned in the case histories. Whenever this is done there are descriptions of acts or words of the patient or observations by physicians that definitely infer the presence of that symptom.

TABLE OF DIAGNOSIS

CASE NUMBER	1	2	3	4	5	6	7	8	9	10	11	12	13
Neurosyphilis of the paretic type	5*	2*	7*	6*	*	4			5	5	3	4	5
Neurosyphilis of the gummatous type	5												
Neurosyphilis of the vascular type		5			2			2	4	3			
Incipient paresis or ''paresis sine paresi''									*	*			
Cerebral arteriosclerosis			4*	6*	5*			3					
Dementia precox											*	3*	
Toxic-exhaustive insanity						3*	*						
Manic-depressive insanity or allied condition											3		
Alcoholic delusional insanity													4*
Unclassified					1		6	*			2	1	
Number of physicians who expressed opinions	5	5	7	6	6	4	6	5	5	5	5	5	6

*Indicates the present classification. Where two occur the case is considered a combined condition.

Figures show the number of physicians who preferred the indicated diagnosis. When two or more possible diagnoses are mentioned in the staff meeting record book and no preference named that physician is here counted as ''voting'' for each condition mentioned by him.

SUMMARY

1. Thirteen cases are presented concerning which there has been more or less doubt as to the correct diagnosis. In all of these cases general paralysis of the insane or vascular neurosyphilis was at least suspected.

2. Four of these cases have come to necropsy. Three more died and necropsy was refused. Two are at home. Four are still under

observation but there is little chance of obtaining necropsy permission.

3. Five have now been classed as paresis, two from autopsy data and three from clinical and laboratory evidence.

4. If Case 2 was really paretic neurosyphilis, the development of mental symptoms within two years of the initial infection and death occurring only two years later are worthy of notice.

5. The other eight cases that resembled paresis are now classified as follows:

Toxic insanity,	
Heart and kidney disease,	Autopsy 1.
Diabetes,	Autopsy 1.
Dementia precox,	Clinical evidence, 2.
Alcoholic insanity,	
Alcoholic delusional insanity,	Clinical evidence, 1.
Incipient paresis,	Clinical evidence, 2.
Unclassified,	Clinical evidence, 1.

6. According to text books published prior to the recognition of syphilis as the necessary causative factor in paresis, these same conditions were often confused with that disease.

7. An analysis of physical and mental symptoms in the individual cases shows close resemblance of these cases to true paresis.

8. The results of serologic tests as tabulated show clear, differential points between paresis and the pseudoparetic conditions.

9. Dementia precox may present symptoms closely allied to paresis but continued observation and repeated serologic tests will usually suffice to remove doubt concerning the true condition.

10. Cases with physical and mental symptoms resembling paresis but associated with severe nephritis, diabetes, failure of cardiac compensation or prolonged alcoholism must be studied carefully before being permanently classed as paresis.

11. Diabetes mellitus may complicate true paresis or may itself cause symptoms simulating paresis. This is demonstrated by Cases 4 and 7.

12. There are occasional cases with positive serologic tests in both the blood and spinal fluid and with symptoms that can be explained either by very early paresis or by some nonsyphilitic condition. Many of these patients live in their homes for an indefinite number

of years without progressive deterioration. Southard's term "paresis sine paresi" appears to be a better descriptive title for these cases than any other thus far suggested.

13. We do not, as yet, know enough about paresis sine paresi to warrant any positive prognosis, and we can only speculate as to the connection between primary or secondary syphilis with laboratory evidence of neurosyphilis, paresis sine paresi and the true neurosyphilitic insanities.

14. The combination of speech disorder, pupillary changes, reflex changes, amnesia, quick-shifting emotions, character change and conduct slump is here observed in all the paretics reported except Case 4 in which the feeble and demented condition of the patient when admitted prevented a proper examination and Case 2 in which there was no paralysis. From 2 to 6 of these 8 cardinal symptoms appeared in the nonparetic cases.

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FULMINATING SYPHILIDE

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From the Leo M. Levi Memorial Hospital

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THE following case has been deemed worthy of brief notation. Because of the short interval between the appearance of the initial lesion and the succeeding symptoms, the variety of lesions presented, and the intensity of the infection, the term "fulminating syphilide" has seemed appropriate.

W. G., white male, aged twenty-four years, was admitted to the Leo M. Levi Memorial Hospital on January 21, 1918. He bore the appearance of one profoundly ill. Patient stated that two days previously he had been able to work although not feeling well, but on the following day he was too ill to leave his bed. He complained of no acute pain in any particular region save for a moderate soreness in the right chest. The temperature was 102°, the pulse 100, respiration 24.

The following history was elicited: Patient is a farm laborer residing in a remote part of Mississippi. Three weeks after his marriage a lesion appeared on the penis which was diagnosed as a hard chancre by his home physician, and treatment instituted. This was nine weeks before his admission to the hospital. He stated that his wife is, and has always been, in good health to the best of his knowledge.

On appearance of secondary symptoms the patient was advised to visit Hot Springs, and had been here about one week before the onset of the acute symptoms. The only previous diseases the patient could remember were "chills and fever" some three years ago.

On examination a small indurated papule was still present on the corona penis, the vestige of the initial chancre. The skin over the entire body (but more pronounced over the back and chest) was covered with reddish brown lesions of the macular type. At the lower third of both tibiæ were well-advanced gummatous lesions about four inches long and one and one-half inches in width, involving the bone.

The chest examination showed an area of dullness about three inches in diameter, just above the right nipple. Otherwise the lung findings were negative.

There was marked liver enlargement, the lower border extending three fingerbreadths below the costal margin, with pain and tenderness on pressure in the gall bladder region.

The clinical course of the disease was characterized by persistent cough with expectoration of copious yellowish, muco-purulent sputum. Emesis of yellow fluid was almost constant, being excited by the ingestion of even small amounts of water. The temperature ranged from 99 to 103, the highest point being usually reached toward evening. Pulse from 90 to 120, and the respirations at no time exceeded 26.

Microscopic examination of the sputum showed pneumococci and staphylococci. Tubercle bacilli could not be demonstrated.

Blood Examination.—Leucocytes, 27,000; polymorphonuclears, 72 per cent; lymphocytes, 20 per cent; large mononuclears, 8 per cent. Repeated Widal tests and examinations for plasmodium malaria were negative. Blood Wassermann was four-plus.

Urine.—Specific gravity 1.030 to 1.032, albumin and a few granular casts.

Spinal Fluid Examination.—(After two weeks.) Cells 5, globulin, albumin, and Fehling reduction normal. Gold curve, 00010000000. Wassermann negative to 2 c.c.

Antispecific treatment was begun on the third day after admission, consisting of intramuscular injections of mercury benzoate, one and one-half grains every second day. After the third injection the temperature gradually subsided to normal, cough was arrested, and emesis ceased. Also beginning evidence of mercurialism appeared and arsphenamine was then administered, 0.6 gm. every fourth day for four doses. This was again followed by mercury benzoate, injections in one-grain doses every second day. Unguentum hydrargyri dressings were daily applied directly to the gummatous lesions on the tibiæ.

All evidences of syphilis disappeared, Wassermann test became negative, and patient was dismissed on March 5.

Here undoubtedly is a case presenting secondary skin lesions, gumma of bone, gumma of lung, and hepatic-visceral involvement, simultaneously and within nine weeks of the appearance of the initial lesion and with the chancre still apparent. Along with this general and acute infection the hirsute areas were spared, and both clinically and as far as the examination of the spinal fluid could show, the nervous system had been neglected by the disease.

It is also noted that the infection which so vigorously attacked its new host was acquired from his wife, who herself offered no visible signs of the disease. Also, that whether or not increased virulence or lack of resistance was responsible for the fulmination of the infection, it responded to antispecific treatment quite as readily as the milder manifestations of syphillis.

I am indebted to Dr. Wm. H. Deaderick for a careful physical examination of the patient and corroboration of the findings.

TWO UNEXPECTEDLY NEGATIVE WASSERMANN REACTIONS

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THE Wassermann test, on which so much reliance is now so justly placed, sometimes turns out unexpectedly negative, as in the two following instances. It is rarer, however, to be able to show that the negative reaction, although clinically confidently expected, was fully justified by the subsequent course of events.

The first of the two instances relates to a case of lichen planus which simulated both syphilis and mycosis fungoides.

A woman, aged fifty-one and enjoying good general health was referred to me by a colleague, January 16, 1914, on account of a cutaneous eruption. Eleven years previously she had had many "lumps" in both breasts, which had cleared up completely under x-rays. She had married in 1890, that is twenty-four years before I saw her. Just after marriage there had been one pregnancy, the fruit of which aborted at two months. There were no subsequent pregnancies. At eighteen years of age she had had a scaly eruption of the outer surface of both forearms.

When I first saw her the skin was ichthyotic, the palms were red and the palmar lines were very marked, but the cuticle was soft. There were light red patches of erythematous eczema over the front of the right leg, some of which were circinate in arrangement. There was much edema of the legs.

There were two groups of large suppurating, crusted, tubercular lesions, one of the anterior surface and the other on the inner surface of the right thigh. The latter group was irritated by horseback riding, but otherwise the subjective symptoms were unimportant. These tubercular lesions resembled the exuberant tubercular lesions of syphilis. The Wassermann reaction, however, was found negative, which naturally cast a doubt upon the diagnosis. The possibility of the lesions being those of mycosis fungoides was recognized, both from the crushed tumors, and the coincident circinate erythema. The absence of the fierce itching of mycosis fungoides, however, had to be considered. On the other hand, as favoring the diagnosis of syphilis, there was the aspect of the lumpy growths, and the occurrence of the single pregnancy interrupted by miscarriage, occurring shortly after marriage. I was so certain of the diagnosis of syphilis that, in discussing the case with a friend, I used the incident as an instance in which the Wassermann test, if trusted, would have led to an erroneous conclusion. In the meantime, as subsequent events showed, I had no idea of the real nature of the disease.

A mixed treatment of bichloride of mercury and iodide of potash was begun, and neosalvarsan (0.90 gm.) was infused intravenously. This infusion was followed by severe pain in the region of the heart; which quickly subsided, leaving no bad effects.

Shortly after this, she returned home, and wrote that the sores were no better, and that the lesions had become intensely itchy. The refractoriness of the disease to antiluetic treatment, the negative Wassermann, and now the extreme itchiness, together with the circinate erythematous lesions on the legs induced a definite diagnosis of mycosis fungoides. Shortly after this she consulted, independently of us, another dermatologist, who came to the same conclusion.

Her general health was not now so good. She had had, for several months, smothering sensations at night with palpitation of the heart. Her pulse was eighty-three, and she had a dull gray complexion and felt out of sorts. In accordance with the diagnosis of mycosis fungoides a course of treatment with x-rays was advised. Subsequently to the radiation the suppurating nodular lesions healed, which appeared to confirm this diagnosis.

During the winter she wrote again to me that she had a generalized outbreak of red, rough, exceedingly itchy patches, which involved the whole cutaneous surface excepting the scalp, face, palms and soles.

December 27, 1916, the patient called upon me very much improved both in regard to the condition of her skin and in her general health, which was rather surprising in a disease which, when it reaches the tubercular stage, usually marches along promptly to a fatal termination. Her improvement had begun and had been maintained while taking hypodermic injections of seven grains of cacodylate of soda every fifth day. This treatment had been instituted the preceding July, and with the exception of a two months' interval, had been maintained ever since, with steadily progressing beneficial results.

Previous to this arsenical treatment she had become so weak that she frequently had to stop what she was doing and sit down. She was reduced to such a desperate condition with this weakness, and with the torment of her skin, that her physician proposed large doses of arsenic, to which she readily assented. For some time after commencing treatment the weak spells would recur in about four days after the last injection, to clear up on taking the injection. Recently the weak spells had not come on at all. During the treatment she lost twenty-seven pounds in weight. Most of the lesions had faded out, leaving brown stains, and those that were present neither itched nor burned.

The diagnosis now was not difficult. There were large flattened, steep edged, deep red substantial papules, with the characteristic glitter, scattered over the front of the right leg, and a few over the inner surface of the right knee, and on the outer surface of the right thigh.

There are two extraordinarily interesting features in this case; the large dose of arsenic and the undoubted beneficial effect of the drug; and the diagnosis.

The large tuberous lesions were hypertrophic lichen planus papules. The typical lichen planus papule is a minute inflammatory neoplasm consisting of densely packed round cells, which often gives both to the eye and to the finger the impression of substantiality, of a substance embedded in the skin. A gigantic papule would therefore naturally give the impression of a tumor, which it did in the present instance. It was this feature and the clouding of the diagnosis by pyogenic infection, which lead to the error. It was also interesting to note the absence of typical lichen planus lesions for such a long time. This is rare, but it occasionally occurs.

In the premycotic stage, the mistake of considering a mycosis fungoides a lichen is not infrequent, and may be unavoidable, as the violently pruritic red patches may be lichenified, and may resemble lichen so closely as not to permit of any other conclusion. In fact it is often called the lichenoid stage (pèriode lichenoide). Furthermore one must always remember that the diagnosis in both diseases is symptomatic. The possibility of a reverse error; mistaking a lichen with gigantic papules for a mycosis fungoides, is, in my experience, never considered. It is a mistake, however, which we have reason to believe is not unique. Years ago, a patient consulted me, suffering from itchy, infiltrated, scaly, circular, red patches which were refractory to any treatment adopted. No definite diagnosis was made. The patient afterwards consulted a man whose diagnostic ability is unquestioned, and who called in three others in consultation. All these men, and still another of equal ability and experience, arrived at the conclusion that the patient was suffering from mycosis fungoides, and warned the relatives of the gravity of the condition. The patient returned to her home city and was cured of her malady by taking a few doses of a medicine prescribed by an irregular practitioner.

The above is recited here to accentuate the possibility of a parallel error to the one made in the case I report. If my patient had not returned at a time when she showed an undoubted lichen eruption, the case would have remained in our opinion as an instance of mycosis fungoides cured by the administration of stiff doses of an arsenical preparation. And some of the cures of mycosis fungoides reported as cured by the administration of arsenic, may have been instances of this very mistake.

AN INSTANCE OF EPITHELIOMA SIMULATING A SYPHILIDE

A religieuse, fifty-seven years of age suffering from a circinate ulcer of the scalp, called on me November 21, 1917.

She said that in 1898, while employed in the Presidio of San Francisco, nursing soldiers returned from the Philippines, she broke out in sores supposed to be boils. The following year she caught erysipelas followed by swelling under the left side of the jaw. In 1911, the present lesion began on the scalp.

When she consulted me there was an ulcer with a walled, serpiginous advancing border, and covered with a fairly thick crust, and there were a number of small erosions also crusted. The entire lesion occupied a bald area, about five centimeters in diameter, lying a little to the right of the median line of the vertex. The history, the heavy crusting, the ulceration and the location, all pointed to lues. The time indicated, six years, was a little long for a syphilitic lesion, but syphilitic lesions do sometimes persist in a given locality, and patients are not always accurate in their estimate of time.

A boric acid (4 per cent) cold cream was prescribed topically, and a bichloride of mercury, iodide of potash mixture internally, and in about fourteen days the raw surfaces were healed, and the disease had made such progress as to justify the diagnosis.

By February 11, seventy-two days after coming under treatment, the lesion was entirely healed, but it was now seen to be a small nodular epithelioma, cicatrizing as it advanced. Scattered over the whole white, smooth, bald surface, on which the disease had advanced, there were a vast number of minute epitheliomatous nodules about 2 mm. in diameter. They were eminently superficial, dome shaped, smooth, and absolutely circular, and had the waxy glitter of epithelial infiltration. The affection had evidently a very low grade of malignancy.

The reason for the negative Wassermann was now quite plain,—the lesion was not luetic, and in all probability the patient never had had lues.

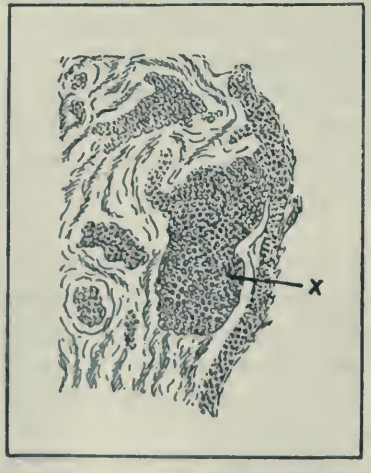

Fig. 1.—*X* shows the epithelial nodule, which by stretching the upper layer of the skin upwards gave rise to the characteristic glistening rounded papule.

This type of epithelioma is quite susceptible to pyogenic infection, which being abated, the incident raw surfaces heal quite quickly. The prompt healing in this case was therefore due to the boric acid ointment, and not to the specific treatment. (Fig. 1.)

The question of mode of treatment now came to the fore. The excision of the affected portion of scalp would have involved a very serious operation, unjustifiable in such a superficial, comparatively mild disease. Curetting, considering the large surface, would also have been too severe. On the other hand its superficiality lent itself especially to treatment with x-rays or radium, and the latter was chosen, with, up to the present, excellent results.

The first case, the lichen planus, is a good example of the difficulties attending a diagnosis when the lesions are of an unusual type, and both this case and the epithelioma show how a diagnosis may be clouded by the intervention of pyogenic infection.

As regards the seroreaction, both are examples of how valuable it is even when negative; when positive its value is, of course, much greater. Indeed it then becomes so valuable that there is often grave danger of allowing it to make the diagnosis.

A FURTHER NOTE ON THE COAGULO REACTION IN SYPHILIS

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SINCE the publication of my first paper with Dr. Kolmer on the coagulo reaction in syphilis[1] in which it was stated that "the preparation of suitable reagents for the coagulo test is at present too frequently disappointing to place the reaction on the basis of a practical routine test for syphilis," I have continued the work with the object of determining and eliminating some of the sources of error, thereby improving the technic.

As stated in the first paper the formation of thrombin is due to the binding of two substances in the blood (serozyme, or thrombin, and cytozyme, or thrombokinase) in the presence of ionized calcium. The thrombin provokes coagulation of fibrinogen present in the oxalate plasma solution of the test. Syphilitic serum when mixed with cytozyme interferes with its activity to a greater extent than normal serum and thereby delays or prevents thrombin production and coagulation.

1. EXPERIMENTS ON THE SEROZYME

One of the causes of the error in the reaction is inclusion of cytozyme in a serozyme; in such a case a control containing diluted serozyme, calcium chloride and diluted oxalate plasma coagulates without addition of cytozyme, which disturbs reaction. A small quantity of cytozyme may not infrequently be present in the oxalate plasma which is carefully prepared avoiding everything which might favor the formation of thrombin. In order to eliminate a small amount of cytozyme contained in oxalate plasma I have adopted the procedure of adding to the oxalate plasma the optimum amount of calcium chloride.

To a series of small test tubes containing five drops of oxalate plasma are added 2, 3, 4, and 5 drops of a 0.5 per cent solution of calcium chloride. Coagulation will result and the time of coagulation will be shortest in the tube containing optimum amount of calcium. Tested by this method the clotting occurred usually first in the tubes containing 2 or 3 drops of calcium chloride. The serozyme now expressed from the coagulum in the tubes containing optimum amount of calcium chloride contains smallest quantity of cytozyme.

TABLE I

TUBE	AMOUNT OF OXALATE PLASMA	AMOUNT OF 1% CALCIUM CHLORIDE	TIME REQUIRED FOR COAGULATION
A	2 c.c.	0. 2 c.c. (1/10 of plasma)	Incomplete
B	2 c.c.	0. 3 c.c. (1, 5/10 of plasma)	7′
C	2 c.c.	0. 4 c.c. (2/10 of plasma)	5′
D	2 c.c.	0. 5 c.c. (2, 5/10 of plasma)	7′
E	2 c.c.	0. 6 c.c. (3/10 of plasma)	10′

Tube A clotted very poorly in one hour and a half, and required 0.1 c.c. more of calcium chloride in order to secure solid clotting. The serozyme was expressed by pressing the coagulum in each tube after standing in room temperature for two hours. The amount of thrombin produced in the presence of calcium as tested by the coagulation of diluted oxalate plasma (fibrinogen), is determined as follows:

TABLE II

DILUTION OF ALC. EXTRACT OF HUMAN HEART	SEROZYME				
	A	B	C	D	E
1:20	1′	1′	1′	1′	1′
1:40	1′	1′	1′	1′	1′
1:60	1′	1′	1′	1′	1′
1:80	1′	1′	1′	1′	1′
1:100	2′	2′	2′	2′	2′
No Extract	2′	16′	20′	12′	13′

The serozyme secured from test tube *C* which had the optimum concentration of calcium chloride indicates the existence of smallest quantity of thrombin, while serozyme *B, D, E,* and especially *A* the quantity of thrombin was greater and the clotting of the oxalate plasma was more prompt.

Occasionally it was found possible with a serozyme containing a little thrombin to render it useful by the addition of acetone in proper quantity. According to my experiments a suitable mixture for this purpose is as follows:

0.85% saline solution	90 c.c.
Acetone	10 c.c.
Serozyme	40 c.c.

The solution is incubated at 37°C. for an hour and used in dose of 0.5 c.c. An example of the variation in time required for coagulation with the two kinds of serozyme is shown in Table III.

TABLE III

THE INFLUENCE OF ACETONE UPON THE THROMBIN CONTENT OF SERUM

SEROZYME	DILUTION OF EXTRACT				NO EXTRACT
	1:20	1:40	1:80	1:160	
Serozyme In Acetone-saline solution.	1. 5′	1. 5′	2′	4′	Entire Inhibition
0.5 c.c. of serozyme diluted with 5 volumes of physiologic salt solution (no acetone)	2′	2′	3′	3′	28′

Up to the present, however, it was difficult to insure uniform results using such methods. As general rule, therefore, it is advisable to secure serozyme without cytozyme from an animal, avoiding everything which might favor the formation of thrombin.

2. EXPERIMENTS ON THE PREPARATION AND DOSE OF THE FLUID TO BE TESTED

Another factor of error in the coagulo reaction is due to the presence of cytozyme in the fluid to be tested. As serum resulting from spontaneous coagulation is always likely to contain cytozyme, which disturbs the reaction, the sera are heated to destroy this element. Under these conditions the question arises how high a serum may be heated to destroy cytozyme without injuring its influence in the coagulo reaction; an inspection of Table IV will readily show the time required to destroy cytozyme.

The fresh sera coagulate without exception and usually within twenty minutes owing to great quantity of cytozyme contained. Heating at 50° C. for an hour diminishes this element slightly, while heating at 56° to 58° C. for an hour is usually sufficient to destroy the blood cytozyme. A prolonged incubation at higher temperature (60° to 65° C.), it seems, can not destroy sufficiently a substance

TABLE IV

THE INFLUENCE OF HEATING SERUM UPON THE COAGULO REACTION

TEMPERATURE AND DURATION OF HEATING	NUMBER OF SERUM	WASSERMANN REACTION	DILUTION OF ALCOHOLIC EXTRACT OF HUMAN HEART				CONTROL (No Extract)
			1:40	1:80	1:120	1:160	
Control (With extract alone)	–	–	2. 5′	3′	5′	6′	fl.
Unheated Sera	No. 1	Negative	7′	9′	11′	12′	16′
	No. 4	Strongly positive	7′	11′	16′	50′	55′
	No. 5	Strongly positive	6′	7′	7′	8′	12′
	No. 6	Strongly positive	5′	6′	6′	7′	12′
Sera heated at 50° C. for an hour	No. 1	Negative	7′	14′	10′	14′	40′
	No. 4	Strongly positive	7′	11′	16′	55′	fl.
	No. 5	Strongly positive	6′	7′	7′	15′	15′
	No. 6	Strongly positive	5′	6′	10′	13′	20′
Sera heated at 56° C. for an hour	No. 1	Negative	12′	18′	27′	38′	fl.
	No. 2	Negative	3′	3′	4′	8′	fl.
	No. 3	Negative	3′	3′	4′	7′	fl.
	No. 4	Strongly positive	7′	15′	16′	55′	fl.
	No. 5	Strongly positive	7′	25′	26′	42′	fl.
	No. 6	Strongly positive	12′	13′	25′	42′	fl.
	No. 7	Strongly positive	3′	3′	8′	10′	fl.
	No. 8	Strongly positive	3′	3′	10′	fl.	fl.
Sera heated at 58° C. for an hour	No. 1	Negative	25′	28′	fl.	fl.	fl.
	No. 2	Negative	3′	3′	4′	8′	fl.
	No. 3	Negative	3′	3′	4′	8′	fl.
	No. 4	Strongly positive	85′	85′	fl.	fl.	fl.
	No. 5	Strongly positive	60′	100′	fl.	fl.	fl.
	No. 6	Strongly positive	70′	fl.	fl.	fl.	fl.
	No. 7	Strongly positive	3′	3′	9′	15′	fl.
	No. 8	Strongly positive	3′	9′	15′	fl.	fl.
Sera heated at 58° C. for 2 hours	No. 2	Negative	3′	3′	5′	10′	fl.
	No. 3	Negative	3′	3′	4′	–	fl.
	No. 7	Strongly positive	3′	4′	9′	–	fl.
	No. 8	Strongly positive	10′	11′	15′	fl.	fl.
Sera heated at 60° C. for an hour	No. 1	Negative	240′	fl.	fl.	fl.	fl.
	No. 2	Negative	3′	4′	4′	8′	fl.
	No. 3	Negative	3′	3′	5′	10′	fl.
	No. 4	Strongly positive	fl.	fl.	fl.	fl.	fl.
	No. 5	Strongly positive	fl.	fl.	fl.	fl.	fl.
	No. 6	Strongly positive	70′	60′	fl.	fl.	fl.
	No. 7	Strongly positive	5′	7′	9′	60′	fl.
	No. 8	Strongly positive	10′	17′	18′	90′	fl.

NOTE: The figures indicate minutes required for coagulation; fl., fluid or absence of coagulation.

present in the blood and known as antithrombin, which antagonizes the action of thrombin. If an overheated serum were used, the antithrombin contained within would inhibit the ordinary process of coagulation, so that the tests yield false positive reactions, namely, a delayed coagulation for considerably longer periods, regardless of whether the serum was from a normal or from a luetic person. On the other hand, even prolonged incubation at 60° C. sometimes fails to destroy the cytozyme and autocoagulation occurs. Brandt[2] found 49 sera of this quality in a series of 509 sera constituting a relatively

Table V

The Influence of Dose of Serum upon the Coagulo Reaction

DOSE OF SERA	NUMBER OF SERA	WASSERMANN REACTION	DILUTION OF EXTRACT				CONTROL (NO EXTR.)
			1:80	1:120	1:160	1:200	
	Control with extr. alone		2′	3′	3′	5′	fl.
0.1	Control w. syphilitic serum	Strongly positive	7′	10′	15′	30′	fl.
0.1	Control w. normal serum	Negative	4′	4′	4′	5′	fl.
0.05	No. 1	Negative	7′	14′	30′	30′	fl.
	No. 2	Strongly positive	7′	20′	7′	47′	fl.
	No. 3	Strongly positive	20′	20′	20′	90′	fl.
	No. 4	Strongly positive	5′	7′	10′	60′	fl.
0.1	No. 1	Negative	8′	20′	60′	fl.	fl.
	No. 2	Strongly positive	8′	25′	90′	fl.	fl.
	No. 3	Strongly positive	40′	125′	fl.	fl.	fl.
	No. 4	Strongly positive	27′	40′	90′	fl.	fl.
0.2	No. 1	Negative	10′	10′	28′	fl.	fl.
	No. 2	Strongly positive	18′	60′	90′	fl.	fl.
	No. 3	Strongly positive	55′	100′	fl.	fl.	fl.
	No. 4	Strongly positive	27′	42′	90′	fl.	fl.
0.3	No. 1	Negative	20′	65′	72′	fl.	fl.
	No. 2	Strongly positive	fl.	fl.	fl.	fl.	fl.
	No. 3	Strongly positive	fl.	fl.	fl.	fl.	fl.
	No. 4	Strongly positive	30′	115′	fl.	fl.	fl.
0.4	No. 1	Negative	20′	fl.	fl.	fl.	fl.
	No. 2	Strongly positive	fl.	fl.	fl.	fl.	fl.
	No. 3	Strongly positive	fl.	fl.	fl.	fl.	fl.
	No. 4	Strongly positive	fl.	fl.	fl.	fl.	fl.

Note: The figures indicate minutes required for coagulation; fl., fluid or absence of coagulation.

high percentage (10 per cent). Briefly therefore, the temperature required to destroy thrombin in serum is too close to the temperature which will inhibit normal coagulation.

In order to determine the optimum dose of serum for the coagulo test, varying doses of sera were added to a constant dilution of the alcoholic extract of human heart, and the formation of the thrombin in the mixtures determined by using the customary quantity of the calcium chloride, serozyme and diluted oxalate plasma. Four sera heated at 58° C. for an hour were used with the results shown in Table V.

As shown in Table V, a large quantity of serum such as 0.3 or 0.4 c.c. distinctly inhibit coagulation of the plasma. If a serum were used in such amounts, all the tests will show false positive reactions, regardless of whether the serum was from a normal or from a luetic person. It may be possible that the antithrombin, which survives a temperature of 58° to 65° C., goes on multiplying with increasing doses of the serum heated at 58° to 60° C. for an hour and that finally the clotting power of normal or negative serum will be overwhelmed by the antithrombin. Even with doses of 0.2 c.c. of serum the interpretation of the results was sometimes rendered more difficult by nonspecific inhibition being observed in normal serum, as Uemura[3] has reported. The most suitable dose of the serum for the coagulo reaction appears to be 0.1 c.c.

3. EXPERIMENTS ON THE PREPARATION OF THE CYTOZYME

The cytozyme, as formerly described, may be secured by extraction from almost any cells or tissues by means of alcohol; in conducting the coagulo test it is supplied by the ordinary alcoholic extract of normal tissue used as antigen in the Wassermann reaction. While various organic extracts may be used in the Wassermann reaction, practical experience has shown that some of these extracts in the coagulo reaction lack sufficient thromboplastic power, so that the phenomenon of coagulation is delayed or does not occur at all with normal or negative serum. In general, it seems, the most powerful thromboplastic substances are best suited as cytozyme. Howell[4] has shown that the active substance is one of the phosphatids corresponding apparently to the fraction which has been designated as cephalin. Fränkel and Thiele[5] have reported that the action of cytozyme virtually originates in the ether soluble fraction which contains a substance like jecorin. I have been interested in studying what extract commonly employed in the Wassermann reaction is most suitable as cytozyme for coagulo reaction and also the influence of the method of preparing an extract upon its availability for the coagulo test. For this purpose several kinds of extracts were chosen and those were employed that were suitable for Wassermann reaction. In Tables VI and VII the results of such studies are given.

Table VI

The Influence of Various Tissue Extracts (Cytozyme) upon the Coagulo Reaction

EXTRACTS	DILUTION OF EXTRACTS	WASSERMANN REACTION				CONTROL WITH EXTRACTS ALONE	
		STRONGLY POSITIVE		NEGATIVE SERA			
		NO. A	NO. B	NO. C	NO. D	FOR NO. A, C, D	FOR NO. B
Serum Control		fl.	fl.	fl.	fl.	fl.	fl.
Alcoholic extract of human heart	1:20	12′	4′	4′	3′	1′	1½′
	1:40	fl.	5′	5′	7′	1′	2′
	1:80	fl.	11′	8′	7′	2′	3′
	1:100	fl.	90′	11′	15′	2½′	3½′
Alcoholic extract of pig heart	1:20	fl.		25′		7′	
	1:40	fl.		35′		7′	
	1:80	fl.		fl.		12′	
	1:100	fl.		fl.		28′	
Alcoholic extract of beef heart	1:20	fl.		30′		9′	
	1:40	fl.		34′		9′	
	1:80	fl.		fl.		13′	
	1:100	fl.		fl.		13′	
Concentrated alcoholic extract of beef heart	1:20	fl.		fl.		fl.	
	1:40	fl.		fl.		fl.	
	1:80	fl.		fl.		fl.	
	1:100	fl.		fl.		fl.	
Alcoholic extract of syphilitic liver	1-20	fl.	5′	15′	fl.	fl.	3′
	1:40	fl.	7′	fl.	fl.	fl.	7′
	1:80	fl.	90′	fl.	fl.	fl.	11′
	1:100	fl.	fl.	fl.	fl.	fl.	68′
Acetone-insoluble lipoids	1:20	fl.	10′	25′	fl.	fl.	9′
	1:40	fl.	10′	fl.	fl.	fl.	14′
	1:80	fl.	fl.	fl.	fl.	fl.	14′
	1:100	fl.	fl.	fl.	fl.	fl.	32′
Cholesterinized alcoholic extract of beef heart	1:20	fl.	5′	9′	fl.	9′	15′
	1:40	fl.	7′	fl.	fl.	20′	16′
	1:80	fl.	90′	fl.	fl.	fl.	17′
	1:100	fl.	90′	fl.	fl.	fl.	32′

TABLE VII

The Influence of Method of Preparing a Tissue Extract (Cytozyme) upon the Coagulo Reaction

ALCOHOLIC EXTRACTS OF HUMAN HEART	DILUTION OF EXTRACTS	WASSERMANN REACTION			CONTROL WITH EXTRACT ALONE
		STRONGLY POSITIVE		NEGATIVE	
		SERUM NO. A	NO. B	NO. C	
Serum control (without extract)		fl.	fl.	fl.	
Incubated for one day	1:20	32′	12′	10′	4′
	1:40	75′	110′	10′	5′
	1:80	75′	fl.	17′	5′
	1:160	fl.	fl.	17′	6½′
Incubated for 2 days	1:20	8′	5′	4′	4′
	1:40	24′	45′	10′	5′
	1:80	42′	fl.	16′	5′
	1:160	fl.	fl.	16′	6½′
Incubated for 4 days	1:20	12′	12′	4′	4′
	1:40	90′	fl.	10′	5′
	1:80	fl.	fl.	30′	5′
	1:160	fl.	fl.	30′	7′
Incubated for 6 days	1:20	15′	22′	11′	4′
	1:40	32′	115′	30′	5′
	1:80	90′	fl.	30′	5′
	1:160	90′	fl.	30′	13′
Incubated for 10 days	1:20	25′	22′	5′	4′
	1:40	32′	30′	30′	5′
	1:80	32′	fl.	30′	5′
	1:160	32′	fl.	fl.	15′
Incubated for 14 days	1:20	55′	115′	40′	4′
	1:40	55′	fl.	fl.	5′
	1:80	60′	fl.	fl.	5′
	1:160	60′	fl.	fl.	9′

The results of these studies have shown:

1. That acetone-soluble lipoids, alcoholic extract of beef heart reenforced with cholesterin, alcoholic extract of syphilitic liver and concentrated alcoholic extract of beef heart were far less sensitive than simple alcoholic extract of human heart. We have found that they frequently give false positive reactions with normal serum.

2. Alcoholic extracts of human, guinea-pig and beef heart muscle serve satisfactorily as cytozyme. The first is especially efficient and is to be preferred.

3. The duration of incubation in the preparation of tissue extract has some influence upon the properties of an extract as cytozyme

for the coagulo test; too prolonged incubation is injurious and influences the cytozyme in the direction of decreased thromboplastic action. The optimum period of incubation in the preparation of these extracts appears to be most probably less than 4 days.

CONCLUSIONS

1. A method is described for determining the proper amount of calcium chloride to be added to oxalate plasma for the preparation of cytozyme containing the smallest amount of thrombin.

2. Acetone occasionally removes thrombin from serozyme and thereby improves the quality of the latter for the coagulo reaction, but the results are too irregular for the routine use of acetone for this purpose.

3. All fresh and unheated serums collected in the ordinary manner contain cytozyme which interferes with the coagulo reaction; cytozyme can be destroyed in whole or part by heating the serum. The optimum exposure appears to be 56° to 58° C. for an hour; higher temperatures as 60° to 65° C. are unsuited as yielding false positive reactions.

4. The optimum or best dose of serum for the coagulo reaction is 0.1 c.c. after heating at 58° C. for an hour; larger doses as 0.3 to 0.4 c.c. inhibit coagulation of the plasma in a nonspecific manner and thereby produce false positive reactions.

5. Of the different extracts of tissues used as antigen in the Wassermann reaction, the best for use as cytozyme in the coagulo reaction is a simple extract of human heart muscle prepared by extracting the tissue with alcohol for a period not exceeding four days.

My thanks are due to Professor John Kolmer for suggestions and aid in the conduct of this investigation.

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A PLEA FOR GREATER CARE IN THE EARLY RECOGNITION OF CEREBROSPINAL SYPHILIS

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THE frequency with which the underlying syphilitic condition is unrecognized or overlooked in individuals found to be suffering from incipient cerebrospinal lues indicates that there still are many physicians who fail to appreciate the fact that a negative history or a denial of infection is not to be taken as excluding such a possibility. Even negative serologic findings are not final, as one of the cases to be reported will disclose. The more closely syphilitic involvement of the nervous system is studied, the more definitely does one learn to take nothing for granted and to accept the exclusion of a syphilitic infection as a causative factor only where some other causative agent is clearly active or where every means of determining the presence of syphilis has been utilized and appears negative. It is only too evident that a physician must be always on his guard when dealing with an agent so widespread in its diffusion and so insidious in its nature. It must be borne in mind that the nervous system and the cutaneous system are derived from the same blastodermic layer and it is to be expected therefore that the former is just as liable to be involved as the latter, and that the treatment of syphilis in the future must take into consideration the reaction of the cerebrospinal fluid as well as those of the skin and blood when deciding whether or not a cure has taken place. It has been proved again and again that individuals in whom the clinical evidences had been removed and the blood reactions negatived, would later return with evidences of syphilitic involvement of the nervous system.

The following case is illustrative of a group where there was not only a negative history as regards infection, but the serologic findings also were negative. This led to a provisional diagnosis of a nonsyphilitic lesion but the therapeutic test brought about complete recovery from the symptoms complained of.

Case I.—Male, age thirty-one, married, no children, occupation insurance work. Family and personal history were negative throughout, except that he had had more or less digestive trouble for years, so-called indigestion consisting of gaseous eructations, sour stomach, uneasiness, at times pain in the stomach, and occasionally so-called sick headaches. These attacks of digestive trouble lasted from several weeks to several months. He had such an attack in the spring of 1917, when he spent several weeks in the country returning apparently well. Several months afterwards it again began to trouble him, commencing with vomiting and pain in the head, the former subsiding in twenty-four hours but the headache persisting and gradually growing more intense. For several days prior to examination, there had been developing a semistuporous state.

Examination disclosed that he could be aroused from his stuporous state fairly easily, could answer questions relevantly and connectedly, but was slow to comprehend and to respond. The left side of his face was more flaccid than the right and was less motile during emotional changes. Movement of the left hand and arm was carried out slowly and with considerable incoordination and the muscular power was decidedly lessened. Joint movement and the sense of position was uncertain and indefinite, while touch and prick of the pin were readily recognized. A similar condition was found in the left leg. The tendon reflexes were more active in the left leg and arm. The plantar reflex was normal. Sensation as regards touch, prick of the pin, and temperature was apparently unimpaired. Pulse rate was 52 per minute with a systolic pressure of 135 mm. and diastolic of 90 mm. The urinary examination was negative. Ophthalmoscopic examination of the eyes showed indefiniteness of the disk outline most marked in upper nasal quadrants with considerable reddish striation, all being more marked in the left eye. Wassermann examination of the blood and spinal fluid was negative. The spinal fluid pressure was somewhat increased. The cell count was 2 per c.mm., protein content and Fehling's reduction apparently normal. A probable diagnosis of brain tumor was made and since the history of infection as well as the serologic findings were negative, it was regarded as nonsyphilitic, probably gliomatous or sarcomatous in nature. It was believed advisable to await the development of more definite localizing symptoms and in the meantime administer some mercury and iodide. He was given 2 grains of gray powder, three times a day and potassium iodide beginning with 10 drops of the saturated aqueous solution and increasing it daily. By the middle of the second week it was becoming apparent that the mental condition was becoming clearer and, there was very little complaint of headache, a better use of the arm and leg and a subsidence of the blurring of the optic disks. The improvement was progressive and within three months the patient was apparently well, and since then has been fully able to follow his usual vocation. With such a clinical history this pathology must unquestionably be considered to have been a syphilitic gumma regardless of a negative history and negative serologic findings.

Case II.—Male, fifty-six, married twenty years, two children both healthy.

At twelve, said to have had cerebrospinal meningitis, then perfectly well until seven years ago when he underwent a slight operation for hemorrhoids. Used alcohol moderately. Reports having had gonorrhea at eighteen, but denies any luetic infection. Family history was negative. During the last five years he had complained of more or less headache mostly frontal and usually worse at night. In the fall of 1917 there developed more or less restlessness, nervousness, and sleeplessness and at times acute transitory pains in the legs below the knees.

About six weeks before consultation there was a drooping of the left eyelid, which came up rather suddenly in what was reported as a stroke of apoplexy, although no loss of consciousness occurred. From this time patient complained of double vision, necessitating his giving up his business activities. Investigation of his business affairs at this time disclosed that they were in a state of considerable confusion and that he had borrowed money heavily from every possible source and that he had spent the money rather freely and injudiciously. Further investigation revealed the information that he had always commanded a fairly high salary, had been a free liver and had always been a free spender so that very little attention was paid to whatever modification of his habits was manifested of late years. At the time of this examination he did not seem to have proper insight into his financial situation, yet the present attitude seems to be but an exaggeration of a tendency manifested even when apparently under normal conditions. Venereal disease was denied. Examination disclosed a ptosis of the left eyelid, paralysis of the muscles supplied by the left third nerve, dilatation of the left pupil, pupillary reaction to light was absent in the left eye, while the right reacted slightly to strong artificial light, and there was marked Romberg swaying, absent patellar and achilles reflexes. A murmur, systolic in time, over both mitral and aortic areas, systolic blood pressure 140, diastolic 85. Rate of heart normal. Wassermann examination of both blood and spinal fluids reported positive. The gold solution protein and cell content were not made. There was no speech or writing defect and no noticeable impairment of memory. He was rather irritable, fidgety, obstinate, and excitable, which were also reported as being traits manifested when conditions were normal. He was given a course of neoarsphenamine and mercury over a period of three months followed by iodide for six weeks and he reports himself as feeling better than for some years and has resumed his usual business activities, being apparently normal in every way so far as the mental condition is concerned. The paralysis of the left eye and eyelid have disappeared, but the loss of pupillary reaction and of tendon reflexes still persist.

Syphilis as a cause of trouble in this case was not considered until after the ptosis and double vision developed; and when it was suggested to the patient, it was bitterly resented; and even yet he asserts that he can not understand how it could be possible and he not have any symptoms previously.

CASE III.—Female, age forty-six, married at twenty-one, gave birth to three children, all in perfect health, no miscarriages. Had pneumonia at fifteen, and typhoid fever at twenty-two, without complications in either illness and with complete recovery. No history of venereal disease. Menopause set in at forty-three since which time patient has not been well. Family history was wholly negative.

The present illness developed gradually and although various physicians had been consulted from time to time all had given the patient and her family the idea that all her complaints were incident to, and the result of, the changes caused by the menopause.

At first there were sharp pains in various parts of the body, transitory in duration, occurring first at one place, then at another, often followed by a local sensitive feeling, lasting for a short time. Later there developed pains between the shoulders which would also come and go. After a couple of years there was numbness in all of the extremities more marked on the left side, and more or less clumsiness and stiffness in their movements, as well as some stiffness in the neck. General weakness gradually became more and more marked. During the past year there has been considerable cramping in the muscles of the left leg and arm and difficulty in controlling the bowel and bladder functions. Of late she has also had some difficulty in swallowing fluids because of a tendency to regurgitate through the nose.

Examination showed considerable emaciation, general muscular weakness, marked ataxia and incoordination in all movements, all more marked on the left side. Absent pupillary reflexes to light, the right being worse than the left, absent patellar and achilles reflexes, marked Romberg swaying, speech and writing impairment characteristic of paresis and marked dementia. Wassermann of both blood and spinal fluid were strongly positive.

When it was intimated to the family what was the probable nature of the diseased condition, it called forth rather bitter denunciation, so positive were they in their own minds that such was an utter impossibility and in this they were in a measure supported by the opinion of a physician whose medical education had been acquired many years ago and whose views in regard to bacteria as a cause of disease were rather hazy, at least. The mental deterioration progressed, the patient was committed finally to the Insane Hospital where she died.

Case IV.—Male, age fifty-six, married, two children both healthy. Never used alcohol to excess, never sick in bed since childhood. About two years ago he began to complain of nervousness and some failure of memory which, however, was never recognizable to those about him. His condition was attributed to overwork, arteriosclerosis, neurasthenia and to digestive trouble, but regardless of whatever treatment he was given he gradually continued to grow worse. During the past year he at times manifested some impediment in his speech. He continued to work until five months ago when he was advised to go south, where he appeared to improve considerably both physically and mentally although it is revealed in close questioning that there was a lack of emotional control and a tendency to excitability and irritability, indifference to, and a lack of, interest in the things about him which was foreign to his normal condition. The night following his return home he was seized with a convulsive attack, becoming unconscious, biting his tongue, frothing at the mouth, the attack lasting several minutes. When he was seen the following morning, the emotional instability was quite marked with some tendency to talkativeness, exaltation, restlessness and overactivity in his movements. While he admitted being a sick man he had no insight into the real condition. Memory in general was fairly good, but judgment and reasoning ability were poor, speech and writing defects were slight and suggestive of paresis.

The physical examination otherwise was negative throughout. The blood and spinal fluid Wassermann examination were both strongly positive and the spinal fluid pressure was considerably increased, globulin increased, cell content 40.

The second night following he had another seizure followed by a condition of collapse, a weak rapid pulse, breathing shallow, difficulty in swallowing, some cyanosis from which he recovered slowly, with the mental condition in a state of confusion.

The nature of the trouble was explained to the family and vigorous treatment was advised, but when informed that a cure could not be definitely promised they hesitated and in the meantime transferred him to a sanitarium where it was promised that the sanitarium treatment would bring about better health, and the opinion given that antisyphilitic treatment was unnecessary. About two months later his death was reported.

This case is illustrative of a group that should always arouse one's suspicion of syphilis as a causative factor. We are gradually learning to recognize the fact that the term ''functional'' nervous disease in the narrower sense is a misnomer. Every abnormal function of the nervous system is based upon some pathology and our failure to ascertain the cause of that pathologic process is due to our lack of knowledge or ability to discover the probable pathology.

Hard work is very frequently given as a cause of so-called neurasthenia, but it is very questionable whether hard work of itself can bring about this. When associated with insufficient rest and improper food, then probably it must be considered; but even here it doubtless is more the improper nourishment or insufficient rest that are more active than the work itself. In this patient, furthermore, while some of the physicians consulted attributed the neurasthenic state to arteriosclerosis, there were no indications of this condition at the time of examination. There was no cardiac enlargement, the heart sounds were apparently normal, the systolic blood pressure 145, the diastolic pressure 85, and the urinary findings were normal. A neurasthenic condition coming on in the middle life in the absence of mental worry or anxiety in the majority of cases means some incipient physical pathology, the most frequent, probably, being syphilis, tuberculosis or arteriosclerosis.

CASE V.—Male, age thirty-one, used alcohol rather freely, admits infection at age of twenty-one for which he took treatment from time to time but at irregular periods. Gonorrhea at twenty-six, lasting several months. Four years ago he began to complain of inability to control the bladder function and some difficulty in walking, particularly on going up stairs, when there was a feeling of the legs giving away at the knee joint, a tendency to stumble when running to catch a car or to step up in getting on. A lessening of sexual power. The use of alcohol was stopped, after which he appeared to improve in every way, but during the past years there developed a clumsiness in the use of the hands in carrying out some of the finer movements, such as playing the piano, etc.

An examination at the time of consultation disclosed pupils contracted, nonreactive to light, marked Romberg swaying, absent patellar and achilles reflexes, slight ataxia in gait with a positive Wassermann of both blood and spinal. Four years later he returned for reexamination complaining of numbness from the knees down and about the rectum and buttocks, a feeling of tightness around the lower abdomen, incontinence of urine, loss of sexual power, difficulty in controlling the bowels, pain under the short ribs after exertion, and a feeing of fatigue after slight exertion.

Examination did not reveal any change in the physical condition except that he was somewhat fleshier, less excitable and emotional, some dullness of sensation in feet, buttocks and perineum with a persisting positive blood and spinal fluid Wassermann. This patient during this interval had received numerous intraspinal and intravenous injections as well as mercury by mouth, inunction, and intramuscularly, and also potassium iodide in as large doses as could be borne. In spite of all treatments, however, the condition progressed and his death was reported about eighteen months after the date of the last examination, illustrating that intensity of treatment is not always a criterion as to an individual's response to treatment.

CASE VI.—Female, age 33, married fourteen years, never pregnant. She had scarlet fever at eight, and diphtheria at ten without any complications. Menstruation began at twelve and is reported as having been normal throughout. For the past year there has developed what the family call a nervousness, characterized by a lessened control of the emotions, greater excitability, a tendency to talkativeness and a lowering of the ethical tone. This led to an operation being advised, and in April, 1918, a laparotomy was performed in which the tubes, all of one ovary and part of the other are said to have been removed. Following recovery from the operation, she was taken to the country and while there was apparently improved. But shortly after the return home the condition complained of became more marked and further medical advice was sought.

Examination at this time disclosed her physical condition was somewhat emaciated. The pupils were unequal but reacted to light and accommodation. The tendon reflexes were very active. Otherwise there were no abnormal physical conditions ascertainable. Mentally she was very emotional and excitable, rather talkative and hilarious suggesting a hypomaniacal state. She had no insight into her condition, asserted repeatedly that there was nothing wrong with her, insisting that she ate well, had a good appetite, slept well and did not need any medicine. She manifested a lack of modesty and was very demonstrative in her actions. The speech and writing was somewhat tremulous and suggestive of the disturbances characteristic of paresis. A serologic examination was advised and both blood and spinal fluid was reported as strongly positive, and the spinal fluid gave the colloidal gold sol curve characteristic of the paretic condition. She was given six injections of arsphenamine every week in increasing doses beginning with .3 mgs. then .45, .6, .75 and two of .9. Mercurialized serum, intraspinally was also given at similar intervals beginning with 1/50 grain bichloride and increasing it to 1/5 grain. The protoiodide was also given orally in 1/4 grain doses three times a day. At the end of this course of treatment there being very little change in the condition, the family declined further treatment and took her to the country again, but the condition growing worse it was found necessary to commit her to the Insane Hospital. There was no history of infection ascertainable in this case and because of the absence of any definite physical evidence suggesting it, the possibility of a syphilitic etiology was not even thought of prior to the above examination.

These few cases serve to illustrate how insidiously often the disturbances arising from a syphilitic involvement of the nervous system may develop. Case 5 is illustrative of a type of involvement which in spite of a most vigorous antisyphilitic treatment pursues a progressive course and it tends to bring up the question whether there is not a danger of doing more harm than good by overtreatment. It is not an unusual experience to find a serologic examination yielding a positive reaction which had previously been negative even while treatment is being carried out, and still more frequently is it found that a negative serology may in a short time again give positive results. While under present methods of treatment and subsequent examinations we are frequently able to bring about a return to negative serologic findings, we have yet to learn to what extent this becomes a permanent state. Before the advent of salvarsan and its representatives in the treatment of syphilis we were frequently lulled into a sense of security by the disappearance of all clinical manifestations following the administration of mercury or iodide or both, only to find them reappearing perhaps in a different form later on, and it is becoming apparent that a similar experience is to be the outcome with the arsenical preparations.

If it should prove to be the case that when once the nervous system becomes involved to such an extent as to manifest physical disturbances, we as yet fail a remedy for its complete elimination, then it should lead us to consider the advisability of utilizing the serologic findings of the spinal fluid as well as of the blood in every case of syphilitic infection when first contracted and not wait until there is other evidence of the nervous system being affected.

THE VALUE OF LABORATORY DIAGNOSIS IN NEUROSYPHILIS*

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NEVER have the opportunities been so abundant as at the present time for the practical application of the methods of precision, afforded by the laboratory, in the diagnosis of syphilitic involvement of the neurospinal axis. The importance of the early diagnosis of neurosyphilis is not yet sufficiently appreciated, and probably will not be until incontrovertible proof of the efficacy of early treatment is established. With the number of persons in the military service at present under an ideal regime, strictly controlled by a discipline only possible in such service, we have a condition that can never exist in civil life for obtaining such proof.

Fordyce[1] states that 10 per cent of syphilitics have nervous involvement according to the old statistics, but it is his view that careful examination with our newer methods would show at least 20 per cent. In 250 laboratory examinations of 75 spinal fluids from a series of syphilitics without objective evidence of neurosyphilis 83, or 33 per cent, showed pathologic findings. The expert clinical opinion of Fordyce, therefore, bears the earmarks of extreme conservatism.

In 967 laboratory examinations of spinal fluids from a series of syphilitics with objective signs of nervous involvement, pathologic findings were present in 787, or 81 per cent. In view of the fact that approximately 20 per cent of those suffering from neurosyphilis

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TABLE I

SHOWING THE INCIDENCE OF PATHOLOGIC FINDINGS IN THE SPINAL FLUID OF SYPHILITICS

	(A) Including Cases with Symptoms of Involvement of the Central Nervous System				
	TOTAL			INCREASED	
	NO.	DIMINISHED	NORMAL	NO.	%
Pressure	178	II	53	114	64
Globulin	215		34	181	84.1
Cell counts	225		67	158*	70.2
Colloidal gold	280		60	220**	78.5
Wassermann	319		122	197***	61.5
Total	1,217			870	71.4
	(B) Including Only Cases Without Symptoms of Involvement of the Central Nervous System				
	TOTAL			INCREASED	
	NO.	DIMINISHED	NORMAL	NO.	%
Pressure	25	I	5	19	76.
Globulin	45		12	33	73.3
Cell counts	57		41	16*	28.
Colloidal gold	55		41	14**	34.1
Wassermann	68		67	1***	1.5
Total	250			83	33.3

*Borderline counts included in this number (6 or more).

**Only those reactions included showing changes greater than I.

***Signifies positive reactions.

do not show pathologic fluids, we are of the impression that it is none too radical to assert that 30 to 40 per cent of those infected with syphilis have foci in the central nervous system, and we are in perfect agreement with Fordyce that these individuals are "potential candidates for one or other forms of neurosyphilis."

If we assume conservatively that 10 per cent of all those infected with syphilis develop some of the *more serious* neurologic sequelæ, that is, tabes dorsalis, paresis, or one of the other forms of neurosyphilis without a classical symptom-complex, but nevertheless equally incapacitating, the inquiring mind must, of necessity, seek the answer to this question: "What proportion of syphilitics would develop those neurological sequelæ if an early diagnosis were made, followed by early, vigorous, and intelligently directed treatment?" The war, despite its destructive features, furnishes an opportunity for its compensations. While millions of our men are sacrificing themselves for humanity, the same system that directs their energies affords the opportunity for a broad and comprehensive demonstration of the effect of early treatment as a prophylaxis of neurologic syphilis. The preservation, for lives of usefulness, of those human beings sacrificed annually at the altar of the Spirochete pallidum might, in some measure, compensate for the loss of others by the bullets of the enemy. Such treatment should be based upon an intelligent interpretation of the combined laboratory and clinical findings, and the results of treatment should be judged in the same manner.

INTERPRETATION OF LABORATORY FINDINGS

From a study of the laboratory findings of over 350 spinal fluids embracing some 1500 examinations we are led to believe that there is a rather definite sequence in the appearence of pathologic changes in the spinal fluid. This sequence, though not invariable, is as follows: (1) increase in pressure, (2) increase in globulin, (3) abnormal colloidal gold curve, (4) pleocytosis, (5) positive Wassermann reaction. With certain limitations each of these factors has a value in differential diagnosis.

PRESSURE

An increase in pressure is, in our opinion, the earliest change to be noted. It is only significant of an altered physiology resulting from some irritation, mechanical, toxic or septic. It occurs just as frequently in the so-called functional states as in conditions resulting from organic lesions. After the period during which the nervous tissues react to the primary irritation, nature accomplishes a readjustment of the pressure-regulating mechanism. In the first stage of meningeal irritation there is usually a great increase in the pressure, which becomes reduced to normal, or occasionally subnormal, as the process becomes more chronic. In parenchymatous lesions, especially paresis, it usually maintains a constant high level. In the so-called functional diseases, such as epilepsy, neurasthenia and the neuroses, it is variable, but corresponds quite well to the symptomatologic remissions.

GLOBULIN

A globulin excess is indicative of an organic lesion and is suggestive, *when persistent,* of parenchymatous involvement of the deeper structures, especially of the encephalon. In such parenchymatous lesions as paresis, taboparesis and encephalitis it is present in from 90 to 100 per cent of cases. In more diffuse lesions of meningoencephalitis it is present in 85 per cent of cases, and in pure meningeal lesions in from 65 to 70 per cent of fluids. The incidence is much lower in pure vascular lesions.

There is one type of lesion in which globulin excess is not only constantly present, but in the highest degree. That is cord compression from whatever cause. This results in the well-known syndrome of Froin, the two most characteristic features of which are marked globulin excess and spontaneous coagulation en masse.

COLLOIDAL GOLD

To a greater extent than any of the other laboratory tests the colloidal gold reaction is of value in the differential diagnosis of paresis. In this disease the reaction is characteristic in from 90 to 100 per cent of cases. At the risk of criticism for indulging in the discussion of a clinical problem we hazard the opinion that general paresis is yet too little understood. If one considers as paresis only the classical symptom complex of the older text writers surely no laboratory is necessary for its diagnosis. The crudest observations make the diagnosis apparent. In this type, which we classify as advanced paresis, a characteristic colloidal gold curve is present in 98 per cent of fluids, e. g., 5555554311. In the absence of such a curve on more than one examination one should be cautious before branding the case as one of paresis. The following case is in point:

L., male, aged 53 years. No history or physical signs of syphilis. Symptoms: Complete disorientation as to time and place. Loss of memory for past and recent events. Lack of insight. Emotional instability. Euphoria.

Physical findings: Argyll Robertson pupils. Romberg. Deep reflexes diminished. Muscular tremors of face and extremities. Thick, slow, and stammering speech. Inability to repeat the ordinary test phrases.

Blood.—Wassermann negative before and after provocatives.

Spinal Fluid.—Negative on three examinations.

The diagnosis of paresis was tenaciously adhered to, and the patient was repeatedly used for clinical demonstrations to students as a classical paretic. In a fashion, too spectacular to relate, the cloudy mentality suddenly began to clear and continued to do so, until the patient approached a normal mental status. It subsequently developed that this patient was a graduate in medicine and had been a drug habitue for many years. Only then was the diagnosis changed to post-drug psychosis.

In taboparesis, with the tabetic symptoms in the ascendancy, the paretic element is frequently overlooked. Its prognostic importance does not require especial emphasis. There is a tendency for the colloidal gold curve in taboparesis to be slightly less intense than in pure paresis of the advanced type, e. g., 5555432100. Type 1, or so-called paretic curves, are found in 88 per cent of fluids.

There is another form of paresis, which we have arbitrarily classified as early paresis, because of the paucity of symptoms. The few paretic symptoms are frequently overlooked in the first clinical examination, to be discovered later, after the laboratory has given a clue to the diagnosis. The complaints of these individuals are most frequently ascribed to neurasthenia. They comprise such complaints as transitory fogging of memory, physical weakness, inability to withstand prolonged concentration and slight impairment of business judgment. Often the only objective clinical evidence is elicited after mental fatigue by prolonged repetition of test phrases and numbers. The first thing that may be noticed is that after the fatigue one or more of a series of six or seven numbers is omitted or misplaced. If the examination is continued longer, it often happens that the test phrases that were repeated correctly in the first instance can not now be repeated without errors. At this stage of the examination it is a common occurrence for the patient to make some such remark as this: "I don't know what the trouble is, but my mind seems to be a blank." In cases of this kind a Type 1 curve occurs in 75 per cent. At the risk of criticism for attempting to place too much importance on the character of curves that accompany this condition, we are bound to suggest that our experience indicates that there is a tendency for these reactions to be less intense quantitatively than in advanced paresis. This is evidenced by the limitation of complete decolorization to the lower dilutions of the spinal fluid, e. g., 5542100000.

There is another class of cases which we consider to be potential paretics; viz., syphilitics with nervous lesions, but with no discoverable evidence of paresis in speech, memory or emotional spheres, but whose fluids show, in approximately 15 per cent, the Type 1 curve. In our efforts to correlate our laboratory results with the clinical findings of unprejudiced observers we are led to conclude that the diagnosis of paresis, in its incipiency, is too frequently missed through failure to apply or to correctly interpret the aids of the laboratory.

Table II

Showing the Incidence of Maximum Color Changes of Colloidal Gold Solutions by the Spinal Fluid in Luetic Diseases

	No. Fluids	Nos. Representing Maximum Color Changes						Per cent of Type 1 Curves
		5	4	3	2	1	0	
Advanced paresis..	42	41	0	0	1	0	0	98.0
Taboparesis.......	25	22	3	0	0	0	0	88.0
Early paresis......	32	24	6	0	2	0	0	75.0
Tabes dorsalis.....	22	3	3	5	7	3	1	14.0
Cerebrospinal lues.	102	18	18	24	27	13	2	18.0
Lues without C. N. S. symptoms....	57	0	2	2	12	31	10	00.0
Total	280	108	32	31	49	47	13	38.5

Table III

Showing the Incidence of Complete Precipitation of Colloidal Gold Solutions by the Spinal Fluids of Paresis

	COMPLETE PRECIPITATION						
	5 or More Tubes	4 Tubes	3 Tubes	2 Tubes	1 Tube	None	Total No.
Advanced paresis.....	25	8	5	3	0	1	42
Taboparesis..........	5	6	1	3	7	3	25
Early paresis.........	2	1	10	8	3	8	32
Total..........	32	15	16	14	10	12	99

CYTOLOGY

The cytology of the spinal fluid is of differential value to the extent that it is an index of the extent of meningeal involvement. Lesions predominantly vascular or parenchymatous are evidenced by a low degree of pleocytosis, 10 to 40 cells. On the other hand, lesions predominantly meningeal are evidenced by a pleocytosis of 100 to 1000 cells.

WASSERMANN REACTION

The Wassermann reaction in the spinal fluid usually becomes positive later than the other tests. One can not obtain a correct idea of the positive incidence of this reaction, unless the fluid is used in amounts as high as 2 c.c. Again, without the employment of an antigen reinforced with cholesterin, the complement-binding property of the fluid will be undetected in 12 per cent of cases.

TABLE IV

SHOWING COMPARISONS BETWEEN THE RESULTS OF WASSERMANN REACTIONS WITH CHOLESTERINIZED AND NONCHOLESTERINIZED ANTIGENS

	CHOLESTERINIZED ANTIGEN			NONCHOLESTERINIZED ANTIGEN		
	No. Fluids	Pos.	%	No. Fluids	Pos.	%
Early paresis	32	31	96.9	32	28	87.5
Advanced paresis	34	34	100.0	34	33	97.0
Taboparesis	19	19	100.0	19	16	84.2
Tabes dorsalis	41	25	60.9	37	13	35.1
Cerebrospinal lues	125	87	69.6	122	63	51.6
Lues without nerve symptoms	68	1	1.5	68	1	1.5
Total	319	197	61.7	312	154	49.3

TABLE V

SHOWING COMPARISONS BETWEEN THE RESULTS OF WASSERMANN REACTIONS WITH 2 C.C. AND 1 C.C. AMOUNTS OF SPINAL FLUID

	WITH 2 C.C. OF FLUID			WITH 1 C.C. OF FLUID		
	No. Fluids	Pos.	%	No. Fluids	Pos.	%
Early paresis	32	31	96.9	32	30	93.7
Advanced paresis	41	41	100.0	41	40	97.5
Taboparesis	25	25	100.0	25	22	88.0
Tabes dorsalis	41	24	58.5	41	17	41.5
Cerebrospinal lues	126	89	70.6	126	78	61.9
Lues without nerve symptoms	61	1	1.6	61	0	00.0
Total	326	211	64.7	326	187	57.4

A uniform and thoroughly controlled technic is required for the Wassermann reaction. In a previous communication[2] we have outlined the technic that we employ. In the case of those medical men who have sought to discredit the Wassermann reaction, as well as other serologic tests applied to the spinal fluid, we are forced to the conclusion that they have not correlated their clinical and serologic findings, or have employed faulty serologic technic. The present need is not so much for new diagnostic technic as for a proper interpretation of the technic that we now have at our disposal. One of us (Cornwall[3]) has previously reported his serologic Wassermann results as correlated with a careful clinical study of the cases in which they were applied. These results are summarized in Table VI.

TABLE VI

WASSERMANN REACTIONS

	No. Cases	POSITIVE REACTIONS	
		BLOOD	SPINAL FLUID
Advanced paresis	45	100%	100%
Early paresis	32	94%	97%
Taboparesis	25	67%	100%
Tabes dorsalis	41	57%	61%
Diffuse neurosyphilis	125	82%	70%
Syphilis without nervous symptoms	68	82%	1 to 2%
Total	336	78%	66%

Larkin and Levy[4] in a comprehensive pathologic study have demonstrated the merits of the Wassermannn reaction in its relation to pathologic lesions of the aorta. Its clinical application has been convincingly shown in a recent communication by Larkin, Levy, and Fordyce.[5] It is unfortunate that some medical men from incomplete evidence should so unhesitatingly attempt to discredit it, and that others without presenting protocols of the cases upon which their conclusions are based should deny the clinical value of all serologic tests.

CASES

The following cases illustrate the decided clinical value of serologic reactions:

DIFFUSE NEUROSYPHILIS.—H. E., male, aged thirty-four. History of syphilis two years before with indifferent treatment.

Symptoms.—Severe headaches. Pains in arms, back and legs. Confined to bed.

Physical Findings.—Pupils unequal, but react to light. Slight nystagmus. Deep reflexes hyperactive. Double ankle clonus and Babinski. Coarse tremors of arms and legs. Thick speech. *Diagnosis of multiple sclerosis.*

Blood.—Wassermann, 4-plus.

Spinal Fluid.—Pressure increased; Wassermann 4-plus to .2 c.c.; globulin, 3-plus; cells, 130; colloidal gold, 1223320000. *Diagnosis revised to diffuse neurosyphilis.*

After treatment over a period of one year, including mercury intramuscularly, arsphenamine intravenously and twelve intraspinal injections of arsphenamine, his neurologic symptoms entirely cleared up; he gained 20 pounds in weight and was able to resume his occupation. The last examination of his blood and spinal fluid showed negative blood Wassermann, negative spinal fluid Wassermann in 2 c.c., normal globulin, three cells and a normal colloidal gold reaction.

TABETIC NEUROSYPHILIS.—V., male, aged thirty-eight; occupation engraver. Syphilitic history dating back twelve years. Patient entered the clinic with two canes, and gave a history of having been incapacitated from his work for two months.

Symptoms.—Classical of tabes, including bladder and rectal crises and girdle sensations.

Blood.—Wassermann 4-plus.

Spinal Fluid.—Pressure normal; Wassermann 4-plus to 1 c.c., with a cholesterin antigen, negative to 1 c.c. with an alcoholic extract antigen; globulin normal; cells 37; colloidal gold 4222100000. After treatment for 15 months, including intramuscular injections of mercury, potassium iodide, twelve injections of arsphenamine and seven intraspinal injections of arsphenamine he was free from his gastric and rectal crises and girdle sensations; he could walk without the use of a cane, and was able to resume his occupation as an engraver. At the last examination the serologic results were as follows:

Blood.—Wassermann negative.

Spinal Fluid.—Wassermann negative, to 2 c.c.; pressure 2-plus; globulin normal; cells 5; colloidal gold 1112210000.

VASCULAR NEUROSYPHILIS.—T., male, aged thirty-five. Negative syphilitic history.

Symptoms.—Right hemiparesis with emotional disturbances characteristic of a lesion of the subthalamic area.

Blood.—Wassermann negative.

Spinal Fluid.—Pressure normal; Wassermann negative with 2 c.c.; globulin 1-plus; cells 9; colloidal gold 1422333000.

The laboratory suggested syphilis as the probable etiologic factor, but the clinical department did not subscribe to this view, although they advised antisyphilitic treatment as an empirical therapeutic measure. The patient was intolerant to arsphenamine, so intramuscular injections of mercury were given, with large doses of potassium iodide. After four intramuscular injections of mercury salicylate the blood Wassermann became 3-plus and remained positive for eight months, when it again became negative. The treatment was continued for fourteen months. At the end of that time the emotional disturbances, characterized principally by uncontrollable laughter, had to a large extent, disappeared, and the hemiparesis was improved to such an extent that it did not interfere with his work.

SYPHILITIC MENINGITIS.—W., female, aged forty-one. History of syphilis of four months' duration. No skin manifestations or involvement of the mucous membranes. Moderate lymphatic adenopathy.

Symptoms.—Dull pain in back and down legs; headaches. There were no neurologic findings, except hyperactive reflexes.

Blood.—Wassermann 4-plus.

Spinal Fluid.—Pressure increased; Wassermann 4-plus to 1 c.c.; globulin 1-plus; cells 49; colloidal gold 4544220000.

The treatment in this case has not been pursued long enough to report the results, but one can anticipate that under intravenous and intraspinal treatment there should be a symptomatic and serologic cure.

PARETIC NEUROSYPHILIS.—B., female, aged forty. History of syphilis of several years' duration, with indifferent treatment.

Symptoms.—General physical weakness, pain in back and legs. Emotional instability.

Physical Findings.—Sluggish pupillary reaction to light, slight Romberg.

Hyperactive deep reflexes.

Clinical diagnosis of syphilis and neurasthenia.

Blood.—Wassermann 4-plus.

Spinal Fluid.—Pressure 2-plus; Wassermann 4-plus to .6 c.c.; globulin 1-plus; cells 27, colloidal gold 5555453200.

Clinical diagnosis revised to paretic neurosyphilis, substantiated by the demonstration of memory and speech disturbances on careful examination.

After 18 months of continuous treatment, intravenously and intraspinally, there was no change subjectively or objectively. There was no change serologically, except that the blood Wassermann became 1-plus and remained stationary.

Contrary to the general impression, paresis, tabes and the other forms of neurosyphilis do not always originate after the lapse of a period of years after the initial infection. They may arise within a few months after the infection is contracted. We have seen one case of paresis seven months after the initial lesion. Conjugal neurosyphilis, contracted from the mate and first manifesting itself by neurologic symptoms, is no longer a rarity in the large neurologic clinics. Fordyce has called attention to this, and has reported a series of over forty cases.

Among the types of neurosyphilis that respond favorably to treatment our series indicates that the Wassermann reaction is affected first. This can be noted when titrations are made in amounts from .2 c.c. to 2 c.c. After this the cell count begins to diminish and usually reaches normal before the Wassermann becomes entirely negative. Following this the globulin content becomes reduced. The colloidal gold reaction is the last to be affected, with the possible exception of the pressure, which is variable in this respect.

PROPHYLAXIS OF NEUROSYPHILIS

One of the great medical problems of this war is the control of venereal diseases. It will be no less a problem after the war is over and the troops return for demobilization. According to Colonel Ebert[6] the records of the Hawaiian Department in peace times show that more than 20 per cent of all admissions and nearly 25 per cent of all time lost to the government from diseases and injury are caused by venereal diseases. As a result of extensive Wassermann surveys, Colonel Vedder has shown that 16 per cent of the white enlisted personnel, 37 per cent of the colored personnel, and 37 per cent of the inmates of the soldiers' home are syphilitic. In addition, he has called attention to the remarkable fact that 16 per cent of 1019 recruits accepted from civil life suffered from undetected syphilis.

It is the undetected syphilitic, the probable harborer of latent spirochetal lesions that, under the rigors of vigorous campaign, is likely to develop neurologic sequelæ. In this event the individual becomes noneffective as a soldier; has a greatly impaired economic value to the civil community, and is a financial burden to the state.

Statistics based upon the serologic examinations of the blood alone are insufficient for the basis of an estimation of the number of persons harboring latent syphilitic lesions because approximately 12 per cent of those with foci in the central nervous system have negative blood but positive fluid serology. Assuming that 16 per cent of recruits suffer from undetected syphilis, we can forsee an army of 320,000 syphilitics among every 2,000,000 men inducted into the service. The difficulties of adequate venereal control increase as troops become mobile and are transported from place to place, which means a rate for the development of new cases in excess of the normal rate of approximately 3 per cent.

Were the problem only to provide adequate treatment in order to keep these men effective and protect their comrades, it would be large enough, but for its ultimate importance to the individual, the army, the state and the race there is a still greater problem. It involves the prevention of those sequelæ which produce their immutable lesions in the delicate structures of the central nervous system.

As previously stated, the potential foci for the development of syphilitic lesions in the central nervous system are implanted during the early stages of the infection. Their presence may be determined by a careful study of the spinal fluid. This examination should be made in every case of syphilis. Thirty per cent of syphilitic fluids will show some pathologic change. Under the ordinary treatment many of them will show a disappearance of the pathology in the spinal fluid, but for that small number that do not show a serologic improvement in the fluid intraspinal treatment should be instituted.

In the detection of nervous syphilis in its incipiency and the early institution of treatment lies the hope of permanently preventing its progress, or in cases where it has gained some headway, of arresting it before irremediable injury is done.

The early recognition of neurologic syphilis, then, is imperative for the following reasons: that the individual may be spared from untold suffering and permanent or semipermanent incapacitation; that the army may not lose his force as a fighter; that the state should not lose his economic services as a producer, and that the state should be saved the expense of his maintenance ten, fifteen or twenty years hence in a hospital, home or asylum.

We consider these as cogent reasons for the plea that every case of syphilis should have a complete study of the spinal fluid and that those cases demanding it should be given intraspinal treatment at the hands of those trained to do this procedure. It is our conviction that neurologic syphilis could be greatly reduced by the following procedures: a lumbar puncture on every case of syphilis; after four to six months of intensive treatment, in positive cases, a second examination of the fluid; institution of intraspinal treatment for those showing positive fluid findings at the second examination; repetition of the lumbar puncture every six months, until a cure or maximum improvement is evidenced by symptomatology and serology.

CONCLUSIONS

Positive serologic findings in the spinal fluid early in a syphilitic infection are common.

They may persist, despite vigorous intravenous or other general treatment, and entirely disappear with the administration of intraspinal treatment.

In the face of these facts the syphilitic has a just reason to demand early diagnosis and early treatment of neurologic lesions before the destructive pathology has proceeded beyond the stage of possible resolution.

TABLE VII

EARLY PARESIS

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
1	PB31	+	+++ 1.0	++++ 2.0	0	0	0	4422110000	
2	PB31	+	++++ 2.0	++++ 2.0	+	4	–	5554321000	
3	PB31	+	++ 1.0	+ 2.0	++	0	+	5543100000	
4	PB31	–	++++ 2.0	+ 2.0	++	41	+	5554421000	
5	PB31	–	++++ 1.0	++++ 2.0	–	8	–	5554432000	
6	PC32	++++	++ 0.5	+ 0.5	–	43	+	5544321100	
7	PC33	++++	++++ 0.6	++++ 0.8	++++	44	+	5555554200	
8	PC33	++++	++++ 0.8	++++ 2.0	++++	6	+	5554532000	
9	PC33	++++	++++ 1.0	++++ 2.0	+++	8	+	2221000000	After 5 intraspinal and 10 intravenous arsphenamines.
10	PL34	0	++++ 2.0	++++ 2.0	0	0	0	5554422000	
11	PL34	0	++++ 0.5	++++ 0.5	0	0	0	4432100000	
12	PP35	++++	++++ 0.2	++++ 0.8	0	74	+	5500000000	
13	PD36	–	++++ 0.6	++++ 2.0	+	21	?	5444323300	
14	PD37	0	– 2.0	– 2.0	+++	12	+	5543332000	
15	PF38	++++	++++ 0.1	++++ 0.2	0	0	0	5554310000	
16	PH39	0	++++ 2.0	++++ 2.0	+	101	+	5553310000	
17	PH39	0	++++ 2.0	++++ 2.0	–	146	+	4443331000	
18	PH39	0	++++ 1.0	++++ 1.0	–	97	0	4443321000	
19	PH40	++	++++ 0.6	++++ 0.6	++	12	++	5534432000	
20	PJ41	–	++++ 1.0	++++ 0.8	+	20	+	4332210000	

TABLE VII—CONCLUDED

EARLY PARESIS

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
21	PJ41	–	++++ 0.8	++++ 0.8	+++	14	+	2222110000	Four intraspinal treatments with salvarsanized serum.
22	PJ41	–	++++ 2.0	++++ 2.0	–	21	+	5543110000	Four intravenous arsphenamines, Hg and KI.
23	PJ41	++	++++ 1.0	++++ 2.0	++	11	+	5552100000	Showing provocative effect of treatment on blood Wassermann.
24	PK42	0	++++ 1.0	? 2.0	+	16		5554432100	Turbid fluid.
25	PK42	0	++++ 0.5	++++ 0.5	N	30	+	4555322111	Cloudy fluid.
26	PK42	0	++++ 2.0	– 2.0	N	132	+	5555530000	Intravenous and intraspinal treatments.
27	PK42	0	++++ 1.0	– 2.0	N	16	+	4443330000	
28	PM43	0	++++ 0.5	++ 0.5	N	58	+	5543210000	
29	PS44	++++	++++ 0.5	++++ 1.0	0	0	0	4553310000	
30	PW45	0	++++ 0.5	++++ 0.5	+	1	+	5221100000	

NOTE: In the "Wassermann" column, "AI" signifies a cholesterinized antigen, and "AII" a noncholesterinized antigen.

TABLE VIII

ADVANCED PARESIS

		SERUM	CEREBROSPINAL FLUID							
			Wassermann							
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
1	PB 2	++++	++++ 0.6	++++ 1.0	++	27	+	5555453200	Salvarsan, Hg and KI. Four intraspinal treatments. Improvement in blood Wassermann and slight subjective improvement.
2	PB 2	+++	++++ 0.6	++++ 1.0	+	0	+	5520000000	
3	PB 2	+++	++++ 0.3	++++ 0.4	+	107	+	5555555410	
4	PB 2	++	++++ 0.3	++++ 0.4	N	15	++	5555555422	
5	PB 2	+	++++ 0.3	++++ 0.4	++	8	+	5555555554	
6	PB 2	+	0	0	Dim.	9			
7	PA 1	++++						5552553210	Postmortem fluid.
8	PB 3	++++	++++ 0.2	++++ 0.1	0	5	++		Salvarsan, Hg and KI. Intraspinal treatment. No improvement. Conjugal infection.
9	PB 3	+++			Dim.	60	++	5555555410	
10	PB 3	++++			++	10	+	5555554431	
11	PB 3	++++	++++ 0.5	++++ 0.2	++	7		5555555200	
12	PC 4	0	++++ 0.5	++++ 0.5	0	0	0	5555531111	
13	PC 5	++	++++ 0.5	++++ 0.5	0	0	0	5555552100	
14	PC 5	0	++++ 0.5	++++ 0.5	0	0	0	5555555543	
15	PC 6	+++	+++ 1.0	++ 2.0	+	7	+	5555321000	Ophthalmoplegia with no improvement under intravenous and systemic treatment.
16	PC 6	++	+++ 1.0	++ 2.0	+	6	+	5555555441	
17	PC 6	+	+++ 1.0	− 2.0	+++	7	+	2221100000	Diplopia disappeared after two intraspinal treatments.
18	PG 7	0	++++ 0.5	++ 0.5	++	125	++++	5555554320	Xanthochromia.
19	PG 7	0	++++ 0.5	++ 1.0	++	250	++++	4554333200	Xanthochromia.
20	PG 7	0	++++ 0.5	++ 1.0	0	0	0	5555555410	
21	PG 7	0	++++ 0.5	+ 1.0	Dim.	204	++	5555544420	
22	PH 8	++++	++++ 0.2	++++ 0.2	++	66	++		

TABLE VIII—CONCLUDED

ADVANCED PARESIS

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
23	PH 9	+	++++ 1.0	++++ 1.0	0	0	0	5555552111	
24	PH 9	0	++++ 1.0	++++ 1.0	0	0	0	5555421000	
25	PH10	++++	++++ 0.4	++++ 0.5	+++	12	+++	5555555110	
26	PJ11	0	++++ 2.0	++++ 1.0	0	0	+	5555553310	
27	PK12	0	++++ 0.2	++++ 0.2	0	34	++	5555555100	
28	PL13	0	++++ 0.5	++++ 0.5	+	74	+		
29	PL13	0	++++ 0.2	++++ 0.2	+	20	++	5555543100	
30	PL14	0	++++ 1.0	++++ 1.0	0	0	0	5555543000	
31	PM15	++++	++++ 0.2	++++ 0.3	0	1	+	5555432000	
32	PM16	++++	++++ 0.4	++++ 0.4	Dim.	351	+++	5555440000	
33	PM17	+++	++++ 0.5		0	0	0		
34	PM17	+	++++ 2.0	++++ 2.0	++++	15	++	5555555421	
35	PO18	0	++++ 0.5	++++ 0.5	0	0	0	5555210000	
36	PP19	++++	++++ 0.5	++++ 0.5	0	74	N		
37	PP19	++++	++++ 0.2	++++ 0.2	0	0	0	5544321000	
38	PR20	0	++++ 1.0	++++ 1.0	+	44	++		
39	PR20	0	0	0	0	0	0	5555553100	
40	PR22	++++	++++ 0.1	++++ 0.2	0	36	++	5555553101	Subjective improvement. No improvement in objective symptoms.
41	PR22	++++	++++ 0.1	++++ 0.4	++	149	+	5544320000	
42	PR22	++++	++++ 0.3	++++ 0.4	++	12	++	5552210000	
43	PS23	++++	++++ 0.5	++++ 0.5	0	76	++	5555553200	
44	PB25	0	++++ 0.5	++++ 1.0	0	0	0	5555432100	
45	PC26	0	++++ 0.5	++++ 1.0	0	0	0	5555544210	
46	PF27	0	++++ 0.5	++++ 0.5	N	76	+	5551100000	
47	PF28	+++	++++ 0.5	++++ 0.5	+++	20	+++	5555421000	
48	PW29	++++	++++ 0.5	++++ 0.5	0	0	0	5552210000	
49	PW30	0	++++ 0.4	++++ 0.4	0	0	0	5555532000	

TABLE IX

TABOPAHESIS

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
1	PB48	++++	++++ 0.5	+++ 0.5	++++	237	++	5555443000	
2	PB49	0	++++ 0.5	++++ 1.0	0	0	0	5555541000	
3	PB50	–	++++ 0.3	++++ 0.5	+	50	+	5433100000	
4	PB50	–	++++ 0.5	++++ 2.0	0	0	0	5543321000	
5	PD52	0	++++ 2.0	++++ 2.0	0	0	0	5543200000	
6	PG53	+	++++ 2.0	? 2.0	N	133	+	5232211000	
7	PH54	+++	++++ 1.0	++++ 1.0	N	88	+	5555421100	
8	PH54	+++	++++ 0.3	++++ 0.5	Dim.	122	+	5555532100	
9	PH54	+++	++++ 1.0	++++ 2.0	N	0	0	4555432110	
10	PH54	0	++++ 1.0	++++ 2.0	0	0	0	4433310000	
11	PH55	++++	++++ 0.5	++++ 0.5	N	12	+	5233100000	Optic atrophy; quiescent.
12	PH55	++++	++++ 0.3	++++ 0.3	+	0	+++	5555543100	Much treatment with relief of subjective symptoms.
13	PH55	++++	++++ 0.2	+ 0.2	N	147	+	5555542100	
14	PH55	++++	++++ 0.3		+++	4	++	5555544311	Wassermann fast.
15	PH56	–	+ 2.0	– 2.0	++	0	+	5444332111	Quiescent.
16	PJ57	0	++++ 1.0	++++ 2.0	0	0	0	5555431000	
17	PJ57	+++	++++ 0.5	+ 1.0	+	5	+	5444420000	
18	PJ57	0	++++ 1.0	? 2.0	+	0	0	5555432111	
19	PJ57	0	++++ 0.5	++++ 1.0	0	0	0	4443210000	
20	PO58	++++	++++ 0.5	++++ 0.5	+	28	+	5433210000	
21	PO59	0	++++ 1.0	++++ 0.8	+	87	+	3343110000	
22	PO59	0	++++ 2.0	++++ 2.0	N	11	+	5432100000	
23	PR60	++++	++++ 0.5	++++ 0.5	0	0	0	5554210000	
24	PS61	++++	++++ 0.3	++++ 0.3	+	126	+	5524210000	
25	PJ21	+++	++++ 2.0	++++ 2.0	0	3	+++	5555321100	

TABLE X

TABES DORSALIS

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
1	TA 1	++++	++ 0.4	++++ 0.6	0	32	++		Quiescent improvement of subjective symptoms.
2	TA 1	++	++++ 1.0	++++ 2.0	+	42	++	4434432100	
3	TA 1	++	++++ 2.0	++++ 2.0	Dim.	21	+	1123321100	
4	TB 2	0	++++ 0.5	+ 0.5	+	0	0		
5	TB 3	0			+	0	++		
6	TB 3	0	− 2.0	− 2.0	0	0	0	0000000000	
7	TC 4	0	? 2.0	− 2.0	+	2	++	2232220000	
8	TC 5	++++	++++ 0.4	++++ 0.6	+	0	++		Bilateral charcot knee joints.
9	TC 5	++++	++++ 1.0	++++ 2.0	N	7	+	0012332110	
10	TC 5	+++	++++ 1.0	? 2.0	N	9	+	1113210000	Conjugal infection.
11	TC 5	++	++++ 2.0	− 2.0	++	25	+	1122210000	Marked subjective improvement.
12	TD 6	−	++++ 2.0	− 2.0	N	29	+	1210000000	Optic atrophy.
13	TD 6	−	++++ 1.0	++++ 2.0	0	0			Arrested progress with cure of subjective symptoms.
14	TD 6	−	− 2.0	− 2.0	+++	7	N	1223210000	
16	TD 7	−	− 2.0	− 2.0	N	6	N	1221100000	Arrested.
17	TH 8	−	++++ 1.0	++++ 2.0	0	0	0	1122100000	
18	TH 8	−	++++ 0.5	++++ 2.0	0	0	0	3444544431	
19	TK 9	−	− 2.0	− 2.0	+	10	+	1332000000	Serologic improvement with persistence of occasional slight pains.
20	TK 9	−	++ 2.0	− 2.0	+++	3	+	5444542220	
21	TK 9	−	− 2.0	− 2.0	+++	2	+	1122210000	
22	TK10	+++	++++ 0.6	++++ 0.6	+	2	+	4354432000	
23	TK11	++	++++ 1.0	− 2.0	0	0	0		
24	TM12	++++	++++ 0.4	++++ 0.4	+	135	+++		Optic atrophy.

TABLE X—CONCLUDED

TABES DORSALIS

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
25	TM12	+	− 2.0	− 2.0	+	17	N	1212100000	Arrested
26	TM12	0	++ 2.0	− 2.0	+++	1	N	1122100000	
27	TP13	−	− 2.0	− 2.0	N	6	N	1110000000	
28	TS14	0	− 2.0	− 2.0	0	0	0	0111000000	
29	TS14	0	− 2.0	− 2.0	0	0	0	1112210000	
30	TS15	0	− 2.0	− 2.0	0	0	0	1110000000	
31	TS16	++	++++ 2.0	++++ 0.6	0	0	0	0142220000	
32	TS16	++	++++ 0.6	++++ 1.0	0	0	0	0133221000	
33	TT17	0	++++ 1.0	++++ 2.0	0	30	++	4221000000	
34	TV18	+++	++++ 1.0	++++ 2.0	0	37	N	4222100000	Incapacitated for all work. After vigorous treatment intravenous and intraspinal, ataxia improved. Walks without cane. Lightning pains and gastric crises absent. Has resumed work as an engraver.
35	TV18	++	? 2.0	? 2.0	+	69	N	2211110000	
36	TV18	?	− 2.0	− 2.0	Dim.	54	+		
37	TV18	+	− 2.0	− 2.0	0	11	N		
38	TV18	?	− 2.0	− 2.0	N	0	N		
39	TV18	−	− 2.0	− 2.0	++	5	N	1112210000	General improvement of nourishment marked.
40	TW19	0	++++ 1.0	++++ 2.0	N	0	0		
41	TG20	−	− 2.0	− 2.0	100	+			

TABLE XI

CEREBROSPINAL LUES

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
1	C 1	0	− 2.0	− 2.0	0	0	0	4422200000	
2	C 2	0	++++ 0.5	++++ 0.5	0	0	0		
3	C 3	+++	++++ 2.0	++++ 2.0	0	0	0		Lues II.
4	C 4	0	− 2.0	− 2.0	+	10	+	1121110000	
5	C 5	0	− 2.0	− 2.0	++++	4	+	2133221000	Optic atrophy.
6	C 6	0	− 2.0	− 2.0	0	1	+		
7	C 7	0	++++ 0.5	++++ 2.0	0	0	0	1111000000	
8	C 8	++++	− 2.0	− 2.0	N	3	+	1122320000	
9	C 9	0	− 2.0	− 2.0	N	14	+	1222100000	
10	C10	0	+ 2.0	− 2.0	0	0	0	1122000000	Neuroretinitis.
11	C11	−	− 2.0	− 2.0	+	20	N	1132210000	
12	C12	++++	++++ 0.5	++++ 1.0	N	44	+	2554311000	
13	C13	−	++++ 1.0	++++ 2.0	0	950	++	0000000000	Lues II; neuroretinitis.
14	C14	0	− 2.0	− 2.0	0	8	+	1110000000	
15	C15	++++	++++ 0.3	++++ 0.3	+	22	N	1110000000	
16	C16	0	− 2.0	− 2.0	N	6	N	4444100000	
17	C17	++++	++++ 0.2	++++ 0.2	+	130	+++	1223320000	Entirely incapacitated. Weakness of arms and legs, severe headaches, nervousness, defective vision and body pains. Conditions grew worse during intravenous treatment.
18	C17	0	++++ 0.4	++++ 0.4	+	126	++	5555441100	
19	C17	0	++++ 0.5	++++ 1.0	++	46	++	2221110000	
20	C17	0	++++ 2.0	++++ 2.0	++	107	+		
21	C17	0	++++ 0.5	++++ 1.0	+++	125	+++	4433222010	
22	C17	0	+ 0.5	++++ 1.0	N	5	N	2223210000	
23	C17	0	++++ 1.0	? 2.0	+	29	+		

TABLE XI—CONTINUED

CEREBROSPINAL LUES

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
24	C17	0	++++ 0.5	++++ 0.5	0	0	0	4443321000	Complete objective, subjective and serologic cure under intraspinal treatment.
25	C17	0	+ 1.0	? 2.0	0	0	0	5551110000	
26	C17	—	— 2.0	— 2.0	0	0	0	0000000000	
27	C18	0	++++ 1.0		0	52	++	1422444220	
28	C18				N	46	++	4223210000	
29	C19	0	++++ 1.0	++++ 1.0	0	0	0		Transverse myelitis.
30	C20	0	— 2.0	— 2.0	0	0	0	1111110000	
31	C20	0	++++ 2.0	2.0	0	0	0	1123332100	
32	C21	0			+++	8	+	4443322100	
33	C21	0	++++ 1.0	++++ 1.0	+++	28	++	5554442200	
34	C22	0	— 2.0	— 2.0	N	10	0		
35	C23	+++	++++ 1.0	++++ 1.0	+	228	+	1000000000	
36	C24	0	++++ 0.5	++++ 1.0	0	0	0	4555543111	Hemiplegia luetica.
37	C25	0	++++ 0.4		0	15	++		
38	C25	0	++++ 0.8		0	14	+		
39	C26	0	++++ 1.0	— 2.0	0	0	0		Congenital.
40	C27	0	++++ 0.5	++++ 0.5	0	0	0	4333210000	
41	C28	0	++++ 2.0	— 2.0	0	0	0	1221000000	
42	C29	0	++++ 1.0	++++ 2.0	0	3	+	1111221000	
43	C30	0	++++ 0.5	++++ 1.0	0	0	0	3222210000	Hemiplegia luetica.
44	C31	+++	— 2.0	— 2.0	0	0	0	4333210000	
45	C32	0	— 2.0	— 2.0	0	0	0	2222100000	Monoplegia luetica.
46	C33	0	— 2.0	— 2.0	0	0	0	2231000000	
47	C34	++++	? 2.0	? 2.0	++++	26	+	1110000000	Hand-paresis luetica.
48	C34	++++	— 2.0	— 2.0	N	11	N	2221100000	
49	C35	——	— 2.0	— 2.0	++	5	+	2223211000	
50	C35	—	— 2.0	— 2.0	++	5	++		
51	C36	++++	++++ 2.0	— 2.0	++++	65	++	1212200000	

Table XI—Continued

Cerebrospinal Lues

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
52	C37	0	++++ 1.0	++++ 1.0	+	33	+		Hemiplegia luetica.
53	C38	++++	− 2.0	− 2.0	0	18	+	2222000000	
54	C39	++++	− 2.0	− 2.0	Dim.	0	+	1233210000	
55	C40	0	++++ 1.0	1.0	0	0	0	4222100000	Lues II.
56	C41	0	− 2.0	− 2.0	+	58	N	2221100000	
57	C42	+++	++++ 2.0	− 2.0	N	9	+		Hemiplegia luetica.
58	C43	0	++++ 2.0	− 2.0	0	0	0	2221110000	
59	C44	++	++++ 1.0	++++ 2.0	0	4	++		
60	C44	++	++++ 1.0	++++ 2.0	Dim.	13	++	1223322000	
61	C44	++	++++ 0.8	+ 2.0	++++	7	+	2223110000	
62	C44	++	++++ 0.8	− 2.0	++	10	+	1112230000	More marked improvement in symptoms than in serology.
63	C44	+	+++ 1.0	− 2.0	+++	3	+	1112200000	
64	C45	0	++++ 2.0	++++ 2.0	0	0	0	4311000000	
65	C46	+++	++++ 2.0	++++ 2.0	0	0	0	1111100000	Hemiplegia luetica.
66	C46	0			0	0	0	0000000000	
67	C47	0	++++ 0.5	− 2.0	0	0	0	3333210000	
68	C47	0	++++ 0.5	++++ 2.0	0	0	0	1122222100	
69	C47	0	++++ 0.5	++++ 2.0	0	0	0	2455555553	
70	C48	0	− 2.0	− 2.0	+	20	+	2220000000	Hemiplegia luetica.
71	C49	0	++++ 1.0	++++ 1.0	0	0	0	4234331100	
72	C50	0			N	33	+		
73	C51	++++	++++ 0.5	++++ 0.5		9	N		
74	C52	−	++++ 2.0	++++ 2.0	+++	103	++	2222100000	Honestly denied infection.
75	C52	++	++++ 2.0	++ 2.0	+	101	++	2222100000	Showing provocative blood Wassermann.

Table XI—Continued

Cerebrospinal Lues

		SERUM	CEREBROSPINAL FLUID							
			Wassermann							
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
76	C52	++	+ 2.0	− 2.0	+	24	+	4431000000	Only symptoms headaches and weakness in one hand.
77	C52	++	− 2.0	− 2.0	Dim.	30	+	1112100000	
78	C53	0	− 2.0	− 2.0	0	0	0	1232210000	
79	C54	++++	+ 2.0	− 2.0	N	3	+		Luetic thrombosis.
80	C54	++++	++++ 1.0	++ 2.0	+	5	+	2222100000	
81	C54	0	++ 2.0	− 2.0	N	0	+		
82	C54	0	++++ 2.0	− 2.0	++	8	+	5554300000	
83	C54	0	+ 2.0	− 2.0	N	3	N	5544321000	
84	C55	0	++++ 0.5	++++ 1.0	0	0	0		Congenital.
85	C56	++++	− 2.0	− 2.0	0	6	++	4332100000	Lues II.
86	C57	++++	++++ 1.0	++++ 1.0	0	18	++		Lues II.
87	C58	0	++++ 0.5	++++ 0.5	+	68	+	5523100000	
88	C58	0	++++ 1.0	++++ 2.0	+	34	+		
89	C58	0	++++ 0.5	++++ 0.5	0	0	+	3333220000	
90	C59	0	++++ 0.5	++++ 0.5	0	0	0	4422220000	Xanthochromia.
91	C60	0	++++ 1.0	++++ 2.0	0	0	0	0111220000	
92	C61	0	− 2.0	− 2.0	Dim.	26	0		
93	C62	0	++++ 0.5	++++ 0.5	N	2	N	1111100000	
94	C63	+++	++++ 1.0	2.0	0	0	0	1111110000	
95	C64	0	− 2.0	− 2.0	0	0	0	1123210000	
96	C65	0	+ 2.0	− 2.0	0	0	0	3320000000	
97	C66	0	++++ 0.5	++++ 0.5	N	36	+		
98	C66	0	++++ 1.0	++++ 1.0	N	26	N	3333310000	
99	C66	0	++++ 1.0	++++ 1.0	N	4	N	1111100000	
100	C66	0	− 2.0	− 2.0	N	0	0	4554332110	
101	C66	0	− 2.0	− 2.0	N	0	0	1121100000	

TABLE XI—CONCLUDED

CEREBROSPINAL LUES

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wasser-mann	Antigen I	Antigen II	Pres-sure	Cells	Glob-ulin	Colloidal Gold	Remarks
102	C67	++++	++++ 2.0	++++ 2.0	0	34	++	5555530000	Lues II; 7 mos. duration.
103	C67	++++	++++ 1.0	++++ 2.0	0	40	+++	5555542000	
104	C68	0	++ 1.0	++ 2.0	0	286	++		Lues II.
105	C69	++++			N	12	++	2110000000	Lues III.
106	C70	++++	– 2.0	– 2.0	0	14	N	2220000000	
107	C70	++++	– 2.0	– 2.0	++	0	+	1221000000	
108	C71	+	– 2.0	– 2.0	N	3	+	2232221000	Cerebral type.
109	C72	++++	++++ 0.5	++++ 1.0	0	0	0	1233210000	
110	C72	++++	++++ 2.0	++++ 2.0	0	0	0	5555543210	
111	C73	++++	++++ 0.5	++++ 0.5	+	0	+		Optic atrophy.
112	C74	0	++++ 0.5	++++ 2.0	0	0	0	1122100000	
113	C74	0	++++ 0.5	++++ 1.0	0	0	0	1234555300	
114	C75	++++	– 2.0	– 2.0	0	11	+	1110000000	
115	C76	–	– 2.0	– 2.0	N	9	+	1422333000	Vascular—Hemiparesis. Blood positive after provocative. Cure with intravenous treatment.
116	C77	0	++++ 1.0	– 2.0	0	0	0	2221000000	
117	C77	0	– 2.0	– 2.0	N	7	+	1122211000	
118	C78	0	++++ 2.0	– 2.0	0	0	0	1122331000	Lues III.
119	C79	–	– 2.0	– 2.0	+	20	+	1222100000	
120	C80	++++	++++ 1.0	++++ 0.8	+	65	+	2224340400	
121	C81	++++	++++ 1.0	++ 1.0	0	260	+++		Lues II.
122	C82	0	++++ 2.0	++++ 2.0	0	24	+	1111000000	
123	C83	–	– 2.0	– 2.0	N	10	+	1112210000	Nocturnal epilepsy. Ataxia; Romberg.

TABLE XII

LUES WITHOUT CENTRAL NERVOUS SYSTEM SYMPTOMS

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wasser-mann	Antigen I	Antigen II	Pres-sure	Cells	Glob-ulin	Colloidal Gold	Remarks
1	L 1	++++	− 2.0	− 2.0	N	5	N	0000000000	Lues II.
2	L 2	−	− 2.0	− 2.0	N	4	±	1111000000	Lues II.
3	L 3	+	− 2.0	− 2.0	0	7	+	1123200000	Lues II.
4	L 3	+	− 2.0	− 2.0	0	3		1222100000	Lues II.
5	L 4	++++	− 2.0	− 2.0	0	6	±		Lues II.
6	L 5	+++	0	0	0	9	0	1111000000	Lues II.
7	L 6	0	− 2.0	− 2.0	0	0	0	1110000000	Lues II.
8	L 7	+	− 2.0	− 2.0	0	1	±	1112000000	Lues II.
9	L 8	++++	0	0	+	3	+		Lues I and II.
10	L 9	−	− 2.0	− 2.0	+++	93	++	1221000000	
11	L10	++++	0	0	+	20	±	1111000000	Latent Lues II.
12	L11	−	− 2.0	− 2.0	+	3	±	0000000000	Lues II; prolonged treat.
13	L12	++++			+	5	+	1111000000	Lues II.
14	L13	++++			0	8	N	1110000000	Lues II.
15	L14	++++	− 2.0	− 2.0	0	3	N	1100000000	Lues II.
16	L15	+++	− 2.0	−.2.0	N	4	+	1100000000	Lues II.
17	L16	0	− 2.0	− 2.0	0	4	N		Lues II.
18	L17	0	− 2.0	− 2.0	0	6	±	1112111000	Lues III.
19	L17	0	− 2.0	− 2.0	0	5	±	0000000000	Lues III.
20	L18	−	− 2.0	− 2.0	0	11		1111000000	Myocardial lesion; treated.
21	L19	−	− 2.0	− 2.0	0	0	0		
22	L20	++++	− 2.0	− 2.0	0	7	0		Lues II.
23	L21	−	− 2.0	− 2.0	+	3	N	0000000000	Lues II.
24	L22	+++	− 2.0	− 2.0	0	1	N	1110000000	Lues III.
25	L23	0	− 2.0	− 2.0	+	0	0	1110000000	Aortitis.
26	L24	+++	− 2.0	− 2.0	++	1	+	1110000000	Lues III.

TABLE XII—CONTINUED

LUES WITHOUT CENTRAL NERVOUS SYSTEM SYMPTOMS

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
27	L25	++++	− 2.0	− 2.0	0	2	N	1110000000	Lues III.
28	L26	−	? 2.0	− 2.0	+++	6	++	4312210000	Torticollis.
29	L26	−	++++ 2.0	+++ 1.0	++	1	+	1112210000	After intravenous provocative.
30	L27	++++	− 2.0	− 2.0	0	0	0	1222210000	Lues II.
31	L28	0	− 2.0	− 2.0	0	3	N	0000000000	Lues II.
32	L29	0	− 2.0	− 2.0	0	9	±		Lues I.
33	L30	++++	− 1.0	− 2.0	0	3	N	1111100000	Lues III latent.
34	L31	++++	− 2.0	− 2.0	0	2	±	1111000000	Lues II.
35	L32	0	− 2.0	− 2.0	0	0	0	1110000000	Lues II. Alcoholism.
36	L33	+++	− 2.0	− 2.0	N	3	+	1110000000	Lues II.
37	L34	++++	− 2.0	− 2.0	+	4	±	1111000000	Lues II.
38	L35	+++	− 2.0	− 2.0	0	4	N	1111100000	Lues III.
39	L36	0	− 2.0	− 2.0	+	19	+	1111000000	Lues I.
40	L37	++++	− 2.0	− 2.0	0	1	N	1110000000	Lues II.
41	L38	++++	− 2.0	− 2.0	+	0	±	2220000000	Lues III.
42	L39	+	− 2.0	− 2.0	+	2	±	1110000000	Lues II.
43	L40	+++	− 2.0	− 2.0	0	3	N		Lues II.
44	L41	0	− 2.0	− 2.0	0	0	0	1111100000	Lues II.
45	L42	− −	− 2.0	− 2.0	0	3	±		Lues II. Much treatment.
46	L43	++++	− 2.0	− 2.0	0	15	±		Lues II.
47	L44	− −	− 2.0	− 2.0	+	4	N	1211110000	Neurasthenia; treated.
48	L45	++++	− 2.0	− 2.0	Dim.	0	±	1110000000	
49	L46	−	− 2.0	− 2.0	+++	4	N	1112210000	Neurasthenia; treated—conjugal.
50	L47	++++	− 2.0	− 2.0	++	54	N	1111110000	No signs of lues—conjugal.

TABLE XII—CONCLUDED

LUES WITHOUT CENTRAL NERVOUS SYSTEM SYMPTOMS

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
51	L48	++++	− 2.0	− 2.0	+	6	N	0000000000	Neurosyphilophobia, severe.
52	L49	+++	− 2.0	− 2.0	0	2	+	0000000000	Lues II.
53	L50	+++	− 2.0	− 2.0	0	0	0	1100000000	
54	L51	0	− 2.0	− 2.0	0	2	N		Lues II.
55	L52	+++			0	3	+	2221200000	Lues; latent.
56	L53	0	− 2.0	− 2.0	0	0	0		
57	L54	+++	− 2.0	− 2.0	0	0	0	4433311000	
58	L55	++++	− 2.0	− 2.0	0	4	±	1100000000	Lues I.
59	L56	++++	− 2.0	− 2.0	0	0	0	0000000000	Lues II.
60	L57	+++	− 2.0	− 2.0	0	2	±		
61	L58	++++	− 2.0	− 2.0	+	9	+	1221100000	Lues III.
62	L59	+++	? 2.0	− 2.0	0	1	N	1221000000	Lues II.
63	L60	−	− 2.0	− 2.0	0	0	0	2211100000	
64	L61	++++	− 2.0	− 2.0	0	3	N		Lues II.
65	L62	++++	− 2.0	− 2.0	0	2	±		Lues II.
66	L63	+	− 2.0	− 2.0	0	0	0	1111000000	Lues II. Interstitial keratitis.
67	L64	++++	− 2.0	− 2.0	0	0	N	1111100000	
68	L65	+	− 2.0	− 2.0	0	3	±		Lues III.
69	L66	0	− 2.0	− 2.0	0	2	+		Lues II.
70	L67	+++			0	13	±	0000000000	Lues II.
71	L68	+++	− 2.0	− 2.0	++	5	N	1110000000	Congenital.
72	L69	−	− 2.0	− 2.0	0	3	±	1122320000	
73	L70	0	− 2.0	− 2.0	+	1		1111000000	Lues II.
74	L71	++++	− 2.0	− 2.0	N	1	+	0000000000	Lues II.
75	MC 8	++++	− 2.0	− 2.0	Dim.	9	+	1112210000	Lues II. Gluteal myositis.

TABLE XIII
MISCELLANEOUS

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
1	MB 3	–	– 2.0	– 2.0	N	452	+	2223221000	Tuberculous meningitis organism in smear.
2	MO 4	–	– 2.0	– 2.0	N	184	+	1112110000	Influenzal meningitis organisms in smear.
3	MB 2	–	– 2.0	– 2.0	0	0	0	2442232100	Streptococcic meningitis.
4	MB 2	–	++++ 1.0	– 1.0	0	0	0	5551000000	Streptococcic meningitis, postmortem fluid.
5	EB 3	–	– 2.0	– 2.0	+	1	±	1121100000	Epilepsy.
6	EJ 9	–	– 2.0	– 2.0	+	5	+	1112110000	Epilepsy.
7	ER11	–	– 2.0	– 2.0	++	3	+	1111000000	Epilepsy.
8	MC 1	–	– 2.0	– 2.0	++	0	±	1221000000	Alcoholic neuritis.
9	MR 2	0	– 2.0	– 2.0	N	27	N	1111100000	Alcoholic neuritis.
10	MR 4	0	– 2.0	– 2.0	+	3	N	1111000000	Alcoholic neuritis.
11	MV 1	0	– 2.0	– 2.0	N	1	N	2311000000	Alcoholic neuritis.
12	MG 1	0	– 2.0	– 2.0	+++	1		5522210000	Psammoma of dura, (A1046).
13	MB14	0	– 2.0	– 2.0	+	2	±	1122200000	Brain tumor.
14	MK 5	–	– 2.0	– 2.0	0	5	++++		Cord tumor. Xanthochromia. Coagulation *en masse.*
15	ML 9	0	– 2.0	– 2.0	Dim.		++++		Cord tumor. Xanthochromia. Coagulation *en masse.*
16	ML 8	–	– 2.0	– 2.0	0	36		0000000000	Multiple sclerosis.
17	MW 5	–	– 2.0	– 2.0	0	0	0	1111000000	Multiple sclerosis.
18	MC 2	–	– 2.0	– 2.0	N	3	N	5543100000	Lateral sclerosis.
19	MN 3	–	– 2.0	– 2.0	N	1	N	0000000000	Progressive muscular atrophy.

TABLE XIII—CONCLUDED
MISCELLANEOUS

		SERUM	CEREBROSPINAL FLUID						
			Wassermann						
No.	Case	Wassermann	Antigen I	Antigen II	Pressure	Cells	Globulin	Colloidal Gold	Remarks
20	MO 1	–	– 2.0	– 2.0	+	3	N	0000000000	Neurasthenia.
21	MS11	–	– 2.0	– 2.0	N	3	++	1110000000	Neurasthenia.
22	MD 7	–	– 2.0	– 2.0	N	22	N	2232000000	Dementia.
23	MK 1	–	– 2.0	– 2.0	+	8	N	0002100000	Hysteria or psychic epilepsy.
24	MJ12	–	– 2.0	– 2.0	+	1	+	2212000000	Hemiplegia.
25	MR18	–	– 2.0	– 2.0	N	0	+	1222100000	Hemiplegia.
26	MS19	–	– 2.0	– 2.0	Dim.	18	++	1221000000	Hemiplegia.
27	MS21	–	– 2.0	– 2.0	N	0	±	1111110000	Hemiplegia.
28	MM 1	–	– 2.0	– 2.0	N	0	W	1111000000	Acute nephritis.
29	ML 1	0	– 2.0	– 2.0	N	2	N	0000000000	Chronic nephritis.
30	MD 2	–	– 2.0	– 2.0	+	9	±	1111111000	Chronic nephritis.
31	MD 3	–	– 2.0	– 2.0	N	7	+	1121000000	Chronic nephritis. Hypertension.
32	MS 4	+++	– 2.0	– 2.0	0	1	N	1201000000	Chronic nephritis. Hypertension.
33	MS13	++++	– 2.0	– 2.0	N	9	±	1221000000	Cardionephritis.
34	MM 2	0	– 2.0	– 2.0	N	4	±	1121110000	Cardionephritis.
35	MD 4	0	– 2.0	– 2.0	+	4	±	0000000000	Chronic plumbism.
36	MM 3	0	– 2.0	– 2.0	N	2	N	1110000000	Diabetes.
37	MF 3	–	– 2.0	– 2.0	+	0	++	4442310000	Arthritis, chronic.
38	MB 5	–	– 2.0	– 2.0	+	1	±	1222100000	Arthritis, chronic.
39	MM 4	–	– 2.0	– 2.0	N	1	N	1111000000	Arthritis, chronic.
40			– 2.0	– 2.0	N	5	N	0000000000	Polyglandular dystrophy.
41	MF 4	0	– 2.0	– 2.0	N	2	±	1111000000	Hypertension.
42	MS 8	0	– 2.0	– 2.0	N	7	+	0000000000	Hemiplegia.
43	MB15	–	– 2.0	– 2.0	0	12	±	1111111000	Eclampsia.
44	MK 3	–	– 2 0	– 2.0	0	0	0	5433211000	Eclampsia.
45	MK 3	–	– 2 0	– 2.0	0	0	0	5433221000	Eclampsia
46	MH13	–	– 2.0	– 2.0	+	2	++	0000000000	No diagnosis.

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CRITERIA AS TO CURE IN SYPHILIS

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A SEARCH of recent publications on syphilis reveals a great paucity of articles dealing with requirements that must be filled before a cure of the disease may be affirmed. The work done deals with the pathology of the disease, with methods of diagnosis or treatment or of various manifestations of it in relation to different medical or surgical specialties. Newer methods of diagnosis and treatment have undoubtedly established new standards that are in use for judging when sufficient treatment has been given but these do not seem to be sufficiently well stabilized as yet to warrant publication. Practical experience shows that the newer methods of treatment have rendered many physicians so enthusiastic over prospects of cure that they have either forgotten or have discarded the dicta of older syphilographers who, while they lacked the refined apparatus for treating the disease that we possess, did have what no one can yet have attained with the newer methods—an extended experience with the remedies at their command and a long period of observation of their patients after treatment had been discontinued.

There are several viewpoints from which the question of cure may be approached. The one most natural to use, because it is the most striking, is the clinical: as the first method that could be used, it has been and still is of great value, but experience has shown that negative clinical evidence is unreliable unless observations are carried out for a very long time and very thoroughly. The laboratory method presents points of delicacy that enlarge our view beyond that attained by clinical work alone; it fails, however, to give us data on which to base estimates of cure unless very carefully applied and over long periods so that it really simply amplifies and extends clinical observation in the large majority of cases. A third method is that carried out postmortem in which the presence of lesions of syphilitic origin are taken as an index of cure: unless spirochetes are demonstrated in these lesions, however, the question of their activity comes up and even when they are found, since the observations of Kon and Watabiki,[1] who found spirochetes in variously diseased kidneys, the identity of all seen as S. pallida may be called into question by critical students. Spirochetes vary greatly in both living and fixed preparations so that discrimination between species in postmorten specimens must be very difficult.

In seeking to establish a standard of cure today, then, there must be taken in consideration: first, an intelligent use, based on late experiences, of whatever clinical and laboratory data can be obtained; and second, a period of observation that will satisfy not only the demands of utility as they are seen today in practice, but which will also conform to the requirements laid down by the older syphilographers whose knowledge of the subject was gained from a wealth of experience and long and intimate observation of their patients.

When a physician has demonstrated the presence of syphilis usually the first question asked by the patients is, "Can I be cured?" and if, as should be the case, the physician replies that he is not certain, the second is, "Can I be treated so as not to convey the disease to others?" This latter question can be answered in the affirmative, for, long before the complement-fixation reaction was applied to the disease as a check on diagnosis and treatment, it was known that after certain conditions were fulfilled, the individual could not transmit the disease to others by contact or to offspring by conception or impregnation although he might suffer from the disease himself.[2, 3]

The laborious investigations of Warthin[4] have demonstrated that cured syphilis is analogous to cured tuberculosis. The essential point lacking in his demonstration is that the pathogenicity of the spirochetes observed by him can not, because of technical difficulties, be proved, although their responsibility for the lesions in which they were found can not reasonably be doubted. This leaves open a loop-hole for the escape of such cases as are clinically cured for long periods and die from some affection not manifestly syphilitic. It is upon such cases that the interest of the practicing physician today centers rather than on the unusual case in which minute foci of spirochetes can be demonstrated postmortem.

Aside from failure to relapse, the birth of a healthy child to one who has been infected with syphilis is the most convincing practical evidence of cure. It is evident then that marriage should exact the most rigorous qualifications from the infected individual. In order, however, to determine with certainty that an individual has not transmitted syphilis to his offspring, the children must be observed until they have passed puberty: this ordinarily requires from twelve to fourteen years after the date of earliest possible conception, longer than modern methods of treatment have been in use, consequently it is necessary to fall back upon standards in vogue before the discovery of arsphenamine, in order to get adequate data as to when a cure may be said to have been effected. For this purpose the material published by Fournier[2] in 1880 may be used. Fournier was an extremist in his views on this subject, mercury had been established as a remedy long enough for data as to its value to have been accumulated, and since that time no great improvement in salts for use or methods of administration, with the possible exception of injections, an advance in technic rather than in method, has occurred while except for accumulation of evidence, no marked advance in diagnosis was made until 1906. His requirements for marriage are five:

1. Absence of existing accidents.
2. Advanced age of the diathesis (three to four years as a minimum).
3. A certain period of absolute immunity consecutive to the last specific manifestations. (eighteen months to two years).
4. Nonthreatening character of the disease.
5. Sufficient specific treatment.

To determine what the present attitude should be, it is necessary to examine each of these requirements, to determine in what regard they can be improved upon by present methods, and in how far they may be disregarded.

1. ABSENCE OF EXISTING ACCIDENTS

To the entire absence of clinical evidence of the disease, however slight, that Fournier demanded, may be added negative laboratory findings, negative complement fixation in the blood, normal cell count, globulin content and colloidal gold curve in the spinal fluid, negative complement fixation in the spinal fluid and negative provocative reaction. Although the luetin test has been shown to lack specificity[5] a negative reaction is a point in favor of complete cure.[6] In this requirement, then, although the evidence is still not absolutely conclusive when taken alone, considerable advance has been made and a fairly positive assertion can be made as to whether or not active syphilis exists.

2. ADVANCED AGE OF THE DIATHESIS

Fournier required three or four years after infection as a minimum before marriage and preferred to wait longer. Even now we can scarce accept less than this in view of the treatment which the average case can secure or will submit to although with frequent negative serologic findings and final negative spinal fluid examination, Thompson[7] feels that he may affirm a cure after three years.

3. A CERTAIN PERIOD OF ABSOLUTE IMMUNITY CONSECUTIVE TO THE LAST SPECIFIC MANIFESTATIONS

An important test of the cure of any infectious disease is the length of time the patient remains free from symptoms after treatment is discontinued: the period of time after which we may cease to expect a relapse from any given disease depends upon the disease itself and on the thoroughness with which treatment has been carried out. In regard to syphilis this can only be learned by careful recording and observation for a number of years of cases of frank infection. Relapse in syphilis has been and is a prominent feature of the disease, and thus this point becomes of utmost importance in establishing the occurrence of a cure. Fournier asks for from eighteen to twenty-four months of immunity without treatment before permitting marriage. Present day authorities are reticent on this subject but since modern methods for detecting relapse are more delicate than any he could use, it is perhaps safe to reduce the time to his minimum. Since relapses do occur after that period, even in well-treated cases,[8] it does not seem safe to reduce it to less than this in any case and it should probably be extended materially in those in whom it is known or suspected that treatment has been poorly carried out.

4. NONTHREATENING CHARACTER OF THE DISEASE

The introduction of modern diagnosis and of arsphenamine has completely upset any idea that Fournier may have had on this point and has raised new issues. The cases reported by Benario[9, 10] and more particularly the case of Nichols and Hough,[11] which proved the parasitic origin of nervous relapse, show the folly of attempting to estimate from presenting symptoms what turn a case may take at any future time, under any kind of treatment. In less striking cases than those cited, this uncertainty is repeatedly shown—the most promising cases suffer relapse first and the most severe, judging from early lesions, go longest without return.

5. SUFFICIENT SPECIFIC TREATMENT

Fournier required the use *of mercury and iodide of potassium* in *doses veritably active and curative by a system of intermittent or successive treatment* during *several consecutive years at the minimum, three or four years.* The changes that may now be made in this requirement are due both to better methods for discovering a relapse and to the introduction of a more powerful remedial agent than mercury or iodide of potassium.

In treating any infectious disease, early and rapid elimination of the infecting agent with as little damage to the host as possible from the treatment used, is the object to be attained. Early eradication means a lessened period of infectivity and perhaps a shorter time under treatment: rapid eradication limits the extent of the lesions produced and lessens, except in so far as they are influenced by location of lesion, the residual symptoms that must remain from the activity of the infecting agent during its period of life within the host.

It has been shown experimentally that arsphenamine is a spirocheticide that leaves remarkably little side effect as compared with other drugs, mercury, as effective as it is[12] and the clinical results of its use are now too much a matter of common knowledge to require reference. It is true that some can see no reason for its use[13] and others believe that it really exerts a harmful influence,[14] but these are isolated instances and not in conformity with the complete evidence on hand.

Arsphenamine is not, however, a remedy to be used carelessly: in addition to care in administration, relapse, particularly in the nervous system, is to be guarded against and the patient observed carefully and frequently. Just how often it should be given until symptoms and signs clear is debatable, but experience has shown that it can be given safely every day for three days[15] if due precautions are observed. A somewhat longer interval, about seven days, will probably suffice in all but exceptional cases, the dosage to vary with the patient and specimen of drug used. Its administration may become an emergency operation of imperative necessity at any time. How much of the drug should be given will depend on the case: there seems to be no good reason for exceeding 0.6 gm. for each 150 pounds of body weight and many excellant reasons for giving less than this amount at one time. Neither is there much evidence to warrant continuing the administration after the lesions present have healed and the laboratory findings become negative or when improvement has ceased to follow injection after a reasonably thorough trial has been given.

Sufficient time has not yet elapsed to learn of its true value. Under the older methods of treatment, paresis and the other late manifestations developed about fifteen years after infection, the intervening years having been spent in enjoying health as good as that of any of the arsphenamine treated cases that are seen today: whether time will show that as high a ratio of late manifestations occur after its use as under older methods can only be conjectured now. If, in 1925 or better 1930, it can be shown that late lesions develop later, giving the patient a longer period of healthy life, or that, if they do occur they are less severe and more amenable to treatment, we may consider the drug an advance, while, if none of these are proved, it must be considered only as an agent for rapid control of symptoms. Some hold that the use of arsphenamine has increased the incidence of nervous syphilis; this is doubtful considering the early stage at which such conditions may be diagnosed now and it has been shown that the remedy for it lies in a more thorough and rapid utilization of the drug.[10]

Mercury has not been superseded by arsphenamine and should be used in every case both early and after the more powerful spirocheticide has controlled the acute features of the infection. Fournier required three years treatment with it; now, in view of the rapidity with which lesions not affected by mercury alone can be cleared up by combined treatment and the promptness with which relapse can be detected, this period may safely be shortened. Definite statements are seldom made on this aspect of the subject. It may be held that a fair time would be six months after all symptoms have disappeared, guarding against relapse and resorting to arsphenamine when it occurs. The method of administration will have to be varied with the peculiarities of the patient. Injections probably act most quickly and certainly, larger doses may be given more safely by inunction, while the pain or inconvenience that these methods cause may make it necessary to treat some cases by oral administration. The choice of a salt can be suited by individual selection, the object being to administer as large doses as can be safely borne by the patient.

The inference is, then, that in every point except that of length of treatment, Fournier's rules for marriage must be followed: modern diagnosis and treatment give advantages in detecting and controlling the disease at any time, that enable the physician of today to make concessions that he could not. Summarized, criteria for cure today include treatment with arsphenamine and mercury until negative blood findings are secured and treatment with mercury for at least six months after this; observation for eighteen months after this with frequent negative blood examinations followed by negative spinal fluid findings. Any relapse should be considered as a reinfection so far as cure is concerned. Even with this it is scarcely possible to assure the patient that he is cured beyond doubt: he should be informed of his chances for cure and told to report at yearly intervals, in the absence of symptoms, for further examinations.

Reinfection is of course not to be taken as a practical standard of cure since it involves a second course of treatment. Too few of the reported cases of reinfection fulfill the requirements demanded by White[16] before accepting its occurrence, to be of value in judging what treatment is necessary for cure. White's requirements are: (1) A demonstration of spirochetes in the chancre or syphilitic lesions, or the blood giving a positive Wassermann in the first attack, and (2) in the second attack, the spirochetes being found from the new chancre which appeared at a different site from the first chancre, and the blood at the same time giving a negative Wassermann reaction.

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SYPHILIS AND ITS RELATION TO INFANT MORTALITY*

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IN considering syphilis in its relation to infant mortality, it is necessary to take into account not only the infant born with this disease; but all infected individuals within the procreating age. If acquired syphilis of adults were prevented or properly managed, there would be no infantile syphilis. In the average syphilitic family, the father is first infected prior to marriage, and at the time of marriage the infection is usually in a more or less latent state. Even in this period of latency the infection is transmissible to the mother who in most instances is entirely unaware of its existence in herself. From the mother the infection is transmitted directly to the product of conception at some period in its prenatal existence, resulting in its death or in its being born with the disease which may sooner or later become manifest. Though abortions, miscarriages, and stillbirths are not usually considered as a part of infant mortality, the consideration of these events as a waste of potenial life is of equal importance to infant mortality. In order to have a comprehensive view of the situation, it is necessary to show by statistical review the prevalence of syphilis among adults, and the effect of this infection upon the product of conception, whether it be by terminating life prior to birth or after birth; or by affecting the morbidity of the first years of life.

Numerous statistical studies have been made as to the prevalence of syphilis, but these have been largely based on hospital or dispensary admissions, which patients are largely from the poorer class. There are available no accurate statistics concerning the prevalence in a true cross section of population. Table I represents the results of such studies among the adults admitted to hospitals and dispensaries in five cities of the United States. Statistics from several hospitals having venereal wards were intentionally omitted.

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TABLE I

WASSERMANN SURVEY AMONG ADULTS ADMITTED TO HOSPITALS AND DISPENSARIES

CITY	NUMBER EXAMINED	NUMBER HAVING POSITIVE WASSERMANN	PERCENTAGE HAVING POSITIVE WASSERMANN
Baltimore[1]	1,080	116	10.8
Boston[2]	4,000	600	15.
Chicago[3]	418	56	13.4
Ann Arbor[4]	2,771	160	5.8
San Francisco[5]	6,995	518	7.4
Total	15,264	1,450	9.5

Vedder[6] reports that 13 per cent of 11,933 accepted recruits in the U. S. Army (1916), 15 per cent of 856 candidates for the police force in Washington, D. D., and about 5 per cent of 3,203 candidates for commission in the army were Wassermann positive. These statistics are the result of Wassermann surveys, and therefore represent the minimum of syphilis in the groups examined. It is worth noting that in the same locality that 5.8 per cent of hospital admissions were found syphilitic by the Wassermann reaction, Warthin[7] found 30 per cent syphilitic by necropsy study. Without citing further statistics, it is evident that a minimum of 10 per cent of the adult males of this country, well or sick, are syphilitic, and it is probable that the commonly accepted figure of 20 per cent is nearer the truth. I know from personal experience that a generous proportion of the fathers of syphilitic children are Wassermann negative at the time the child is brought for treatment.

Though the statistics for unmarried women generally show a low incidence of syphilis (3 to 4 per cent) this fact need not concern us to any great extent because of the fact that after marriage the proportion of women having syphilis again approaches that for

TABLE II

WASSERMANN SURVEY AMONG MARRIED PREGNANT WOMEN

	NUMBER EXAMINED	PER CENT HAVING POSITIVE WASSERMANN
Chicago[8]	116	10.6
Brooklyn[9]	1,822	8.
Brooklyn[10]	892	7.9
Philadelphia[11]	40	7.5
New York[12]	2,488	11.5
	5,358	9.66

men. Table II shows that among 5383 married pregnant women in four cities of this country 9.66 per cent were syphilitic as shown by the Wassermann reaction.

The statistics just enumerated show a wide prevalence of a disease having a marked effect upon the infant mortality, infant morbidity, and the birth rate. That some marriages among syphilitics remain sterile because of this disease is certain; but that syphilis plays an important role in sterility is far from proved. As will be seen from tables elsewhere in this paper, certain syphilitic groups studied show a greater fertility than nonsyphilitic families of the same class. Nine per cent of the marriages studied by Raven[13] remained sterile while 32.5 per cent of the marriages studied by Haskell[14] among individuals who later became paretic remained sterile. Raven's figure is within the normal limit while Haskell's is exceptional.

When conception has taken place, the effect of maternal infection upon the product of conception is dependent to a large extent upon the duration of the pregnancy at the time of fetal infection. The infection of the germ cell, if such an event ever occurs, would preclude the possibility of its further development. The earlier in pregnancy the infection of the fetus, the more likely is that pregnancy to terminate in a dead or nonviable infant. The birth of a viable syphilitic infant signifies its infection late in pregnancy. The time at which fetal infection occurs is dependent upon the activity of the infection in the mother and this in turn is dependent to a large extent upon the time elapsed since the onset of her infection. In many instances an untreated mother has given birth to nonsyphilitic children ten years or more after her infection. It has become a well-recognized fact that syphilis is the largest single cause of the death of the fetus at or before term. Stillbirths have averaged in the neighborhood of 5 per cent of all births wherever studied, and at least one-third of this number is due to syphilis. [15, 16, 17, 18] A compilation of statistics (Table III) shows that of 4148 pregnancies in syphilitic families 1258 or 30 per cent resulted in the death of the fetus at or before term. That this is more than three times greater than what might be considered the normal waste of life at this early age is shown by a similar study among the poorer class in both St. Louis and London, and including no obvious syphilis (Table IV). In St. Louis 9.9 per cent of 886 pregnancies and in London 9.4 per cent of 826 pregnancies resulted in the death of the fetus at or before term. Though there may be some doubt as to syphilis being a frequent cause of sterility, there is no doubt that it is a fairly frequent cause of childless marriages.

TABLE III

SHOWING THE FREQUENCY OF FETAL DEATH IN SYPHILITIC FAMILIES

	FAMILIES	TOTAL PREGNANCIES	MISCARRIAGES AND STILLBIRTHS	PER CENT
Holt[19]	193	427	123	28.8
Love[20]	21	172	32	18.6
Harman[21]	150	1,001	172	17.2
Jeans[22]	100	331	131	40.
Jamieson[23]	71	253	95	37.5
Hochsinger[24]	134	569	253	44.4
Raven[13]	82	350	101	28.9
Post[25]	30	168	53	31.6
Haskell[14]	58	167	44	26.2
Tarnier[26]	42	90	56	62.
Julien[27]		206	44	21.4
Pileur[28]		414	154	37.
		4,148	1,258	30.3

TABLE IV

SHOWING THE FREQUENCY OF FETAL DEATH IN A GENERAL SURVEY AMONG FAMILIES SHOWING NO OBVIOUS SYPHILIS

	FAMILIES	TOTAL PREGNANCIES	MISCARRIAGES AND STILLBIRTHS	PER CENT
Jeans and Butler[17]	200	886	88	9.9
Harman[21]	150	826	78	9.4
	350	1,712	166	9.7

Though syphilis is a frequent and well recognized cause of premature birth, there is but little statistical evidence in the literature as to the role it plays. Adair[29] states that of 50 premature infants observed in Minneapolis, 9, or 18 per cent, were proved syphilitic. Prematurity occurred but 8 times in 886 pregnancies in 200 St. Louis families in which there was no obvious syphilis, while it occurred 10 times in 453 pregnancies in 100 syphilitic families, showing an incidence 2½ times greater in syphilitic than nonsyphilitic families, and indicating that syphilis is the most frequent cause of this event.[17] The mortality among premature infants is relatively high whether with or without syphilis. When the problem of maintaining the nutrition and body heat of a premature infant is added to by a syphilitic infection, the outcome is much less hopeful.

There is in the literature a scarcity of statistical studies bearing on the incidence of syphilis in the infant population of this country. Because of the high mortality connected with syphilis in infancy, the group studies among older children or among groups containing older children give an incidence much lower than is to be found in infancy. In St. Louis clinical study was made of 854 infants of one year or under, and Wassermann reactions were made on all infants whose family history, personal history or examination gave any suspicion of syphilis.[17] Of the 854 infants studied, 42, or 4.9 per cent, were found to be syphilitic. This figure represents the minimum in this group because it was not a complete Wassermann survey. In New York Holt[30] found 6.2 per cent positive Wassermann reactions among 161 infants under 2 years of age. Holt's series was selected to the extent that it contained no clinical syphilis, but did contain a certain number of infants whose history or examination gave a suspicion of syphilis. Commisky[9] reports that of 1074 newborn babies in Brooklyn, 3.2 per cent gave positive Wassermann reactions. Because of the frequency of a negative Wassermann reaction in a syphilitic newborn baby, such a study, though interesting, does not represent the true incidence of syphilis. It would seem safe to assume an incidence of about 5 per cent for syphilis in our infant population.

It is somewhat difficult to arrive at the incidence of syphilis in the offspring of syphilitic families for the reason that at the time of such a study usually many of the children are not living and the history as to syphilis is uncertain. In a St. Louis study[22] all the living children of 100 syphilitic families were examined and 78 per cent found to be syphilitic. In a similar study Mott found 58 per cent and Harman 65 per cent to be syphilitic, though Harman[21] states that he accepted the statement of the parents as to the health of many "healthy" children not examined by him. It would seem fair to assume that an average of 75 per cent of the living children in a syphilitic family are infected.

Perhaps of equal interest in this connection is the proportion of the pregnancies in syphilitic families that result in living nonsyphilitic children. Among 2450 pregnancies of our own and collected cases, 408, or 16.6 per cent, resulted in children who were living at the time of the study and found to be nonsyphilitic. This is but slightly more than one-fifth of the healthy living children to be found in a similar study among an equal number of pregnancies in nonsyphilitic familes.

TABLE V

A SURVEY OF THE LIVING CHILDREN IN SYPHILITIC FAMILIES

	FAMILIES	PREGNANCIES	LIVING SYPHILITIC	LIVING HEALTHY	PERCENTAGE OF PREGNANCIES RESULTING IN HEALTHY LIVING CHILDREN
Mott[31]	34	175	41	30	17
Harman[21]	150	1,001	390	210	21
Jeans[22]	100	331	116	33	10
Julien[27]		206	50	43	21
Post[25]	30	168	—	39	23
Hochsinger[24]	134	569	—	53	9.3
		2,450		408	16.6

TABLE VI

A SURVEY OF THE LIVING CHILDREN IN FAMILIES SHOWING NO OBVIOUS SYPHILIS

	FAMILIES	PREGNANCIES	LIVING HEALTHY	PERCENTAGE OF PREGNANCIES RESULTING IN HEALTHY LIVING CHILDREN
Jeans and Butler[17]	200	886	669	75.5
Harman[21]	150	826	634	79.2
		1,712	1,303	76.

A consideration of the mortality in infancy in connection with vital statistics is practically useless because of the current attitude of secrecy toward this infection. However, it may be worth mentioning that 3½ per cent of the infant deaths among the living births in St. Louis have been attributed to lues.[17]

TABLE VII

SURVEY OF EARLY DEATHS AMONG LIVING BIRTHS IN SYPHILITIC FAMILIES

	FAMILIES	LIVING BIRTHS	DIED EARLY	PER CENT
Post[25]	30	168	64	38.
Jeans[22]	100	200	51	25.5
Harman[21]	150	829	229	27.6
Julien[27]		162	69	39.5
		1,366	412	30.2

A survey of about 300 syphilitic families in which there occurred 1366 living births shows that 30 per cent of these infants died at an early age. These infants were not observed and the cause of death is unknown.

A similar survey of 350 presumably nonsyphilitic families shows that of 1489 living births 15 per cent of the children died early.

TABLE VIII

SURVEY OF EARLY DEATHS AMONG LIVING BIRTHS IN FAMILIES SHOWING NO OBVIOUS SYPHILIS

	FAMILIES	LIVING BIRTHS	DIED EARLY	PER CENT
Harman[21]	150	732	94	12.8
Jeans and Butler[17]	200	757	129	17.
		1,489	223	15

Since syphilis is the only known factor of difference between these two groups, it would seem that the infant with syphilis has just half the expectation of life as does a nonsyphilitic infant, leaving out of consideration all other factors. This would also allow us to infer that 15 per cent of the children born in syphilitic families die not necessarily directly of syphilis, but on account of this infection. As a matter of fact, group studies of clinically syphilitic infants show a much higher mortality than this, varying from this figure to as high as 95 per cent in certain unfavorable groups. Hochsinger[32] among 263 infants, gives a mortality of 20 per cent in the first 2 years while Heine[33] gives a mortality of 45 per cent in 100 infants. Of the more recent reports in this country, Holt[34] among 32 infants found a mortality of 12½ per cent due directly to lues and of 37½ per cent due to other causes while the Wassermann was still positive, making a mortality of 50 per cent due to or associated with syphilis. In a St. Louis study[36] we found similarly a mortality of 40 per cent in 100 syphilitic infants. The normal death rate for infants, of the same social class, is about 15 per cent of the births, so that a mortality of 40 to 50 per cent among syphilitic babies represents a mortality of 25 to 35 per cent due to syphilis. In marked constrast to these figures are those of Sylvester[35] who had in 50 infants an immediate mortality of 8 per cent and no ultimate mortality. All such studies in children's hospitals or clinics of necessity leave out of consideration those infants dying while under obstetric care. Commisky[9] reports that 15 per cent of the children born alive to Wassermann positive mothers die before 10 days of age as compared with 3½ per cent of the children born alive to Wassermann negative mothers. From these figures it is seen that syphilis in infancy causes a mortality of at least 15 per cent among the living births in syphilitic families, and that 25 per cent as a general mortality rate among clinically syphilitic infants would be a conservative estimate.

The prognosis in a syphilitic infant depends upon several factors, including the severity of the infection, the type of feeding, and the state of nutrition. In studying the family conditions revealed by the birth and death certificates in St. Louis,[17] it was found that in the families represented by infants which were born alive, but which later died of syphilis, 59 per cent of all the children born in these families are now dead. In the families represented by the stillbirths, 81 per cent of all the children born are now dead. Stillbirths represent a greater severity of infection than in the case of an infant born alive. Infants who show clinical syphilis at birth rarely live more than a few weeks regardless of all other factors. On the other hand, an infant may appear more than usually robust and its only symptom of syphilis be a positive Wassermann reaction. Such an infant has about an equal chance as to surviving the period of infancy as a nonsyphilitic infant.

In certain cases, syphilis may not be severe enough to determine the death of the infant if such an infant is nursed at the breast; but if artificial feeding is resorted to, the nutritional factor in addition to the infection causes death. It is very significant that 80 per cent of the deaths among our St. Louis syphilitic babies have been among those who were breast fed but three months or less.[36] Stating this in another way, the mortality among the infants artificially fed was 60 per cent, while among those breast fed was but 16 per cent. A survey among the older syphilitic children reveals the fact that but 15 per cent of them had been artificially fed in infancy, while a similar survey among older children of a nonsyphilitic group from the same class of patients showed that 28 per cent had been artificially fed in infancy. Almost twice as many nonsyphilitic children survived on artificial feeding as did syphilitic children. So far as the immediate outcome is concerned, the continuance of breast feeding and maintenance of nutrition is of importance, equal to, or greater than, specific medication. Syphilitic babies are usually much undernourished when first seen by the physician. As compared to the normal infant, a large group of syphilitic babies in our clinic averaged 3 pounds under weight.[36] So frequent is this finding that malnutrition is to be regarded as one of the symptoms of infantile syphilis.

Death in a syphilitic infant may result from the infection alone, from a progressive malnutrition, or because of a lowered resistance and accidental intercurrent disease. Often all three factors are concerned. Because an infant dies of pneumonia does not mean that syphilis played no part in the outcome. Most of the deaths occur under 10 months of age, and the mortality is appreciably lowered after 7 months.[36]

RESUME OF THE STATISTICS JUST REVIEWED

From 10 to 20 per cent of adult males and about 10 per cent of married women are syphilitic and a minimum of 10 per cent of marriages involve a syphilitic individual.

Seventy-five per cent of all the offspring in a syphilitic family are infected.

In a syphilitic family 30 per cent of the pregnancies terminate in death at or before term, a waste three times greater than is found in nonsyphilitic families.

Thirty per cent of all the living births in a syphilitic family die in infancy as compared to a normal rate of 15 per cent in the same class.

Probably 25 to 30 per cent of clinically syphilitic infants die as a result of syphilis.

But 17 per cent of all the pregnancies in syphilitic families result in living nonsyphilitic children who survive the period of infancy.

About 5 per cent of our infant population is syphilitic.

According to St. Louis vital statistics, 3½ per cent of all infant deaths are ascribed to lues.

It is admitted that other statistical reviews will, no doubt, give somewhat different results; but the magnitude of the importance of syphilis will remain essentially the same, one of the largest if not the largest public health problem. Even those who think that infant mortality from syphilis in a community is relatively insignificant must agree that as a social and economic problem in a syphilitic family, it assumes a maximum importance when 75 per cent of the pregnancies result in syphilitic offspring, when one-fifth of these die at or before term from the infection, when one-fourth of those born alive die in infancy as a result of syphilis, and when only one-sixth of all the pregnancies result in nonsyphilitic children who survive the troubles of infancy. The waste in infant and child life in a syphilitic family is over 60 per cent as compared to less than 25 per cent in a nonsyphilitic family of the same social plane. Neither should be left out of consideration the morbidity among the living, the mental stress of the parents and the many months of medication necessary for the treatment of the living.

Neither is syphilis as unimportant to the community as many seem to believe or as the vital statistics would indicate. It is fully as important as an agent in destruction of infant life as tuberculosis, and when fetal deaths are taken into account it is of much greater importance. From an analysis of the statistics of the Registrar General, Osler[6] estimated that, including stillbirths and early deaths of infants, the number of actual deaths from syphilis among all ages was of such a magnitude as to place syphilis an easy first among the infections as a cause of death instead of the tenth place it had been given in the report. Downing[6] in a similar estimate from the vital statistics of Massachusetts shows that syphilis falls but little behind tuberculosis as a cause of death.

It is quite probable that we will shortly see an increase of syphilis in the general population as a result of the war. That syphilis has always been increased during war and during the period immediately following a war is a well-recognized fact, and statistics so far compiled show that the present war is no exception.[37] Because of the vigorous measures adopted, the increase will probably not be as great in this country as would otherwise have been the case. The personal prophylaxis with penalties for noncompliance,[38] the restricted zones barring prostitutes, the prompt energetic treatment of infections, the abolition of alcohol, the laws newly passed by most of the states in regard to the control of carriers, and the educational campaign among the enlisted personnel will no doubt have considerable effect in not only lessening the increase of infections, but also in paving the way in an abnormally rapid manner for future profitable public health control of syphilis. For the proper control of syphilis, it is necessary to consider the problem from the standpoint that it is a communicable disease rather than as a social or moral problem. The primary point of attack in the prophylaxis of infantile or any other variety of syphilis is the adult carrier. For such carriers to be controlled means that their whereabouts must be known and this in turn means enforced morbidity reports. The quarantine of such carriers may be carried out theoretically by instruction or actually by probation or commitment and in such a manner that treatment continues[39]. In order that proper treatment be secured, the establishment of clinics by health authorities and the increase of hospital facilities for this purpose will doubtless be found necessary. If the control depended entirely upon enforced legal measures, it would surely meet with failure. It must also depend upon the education of the public in the risks and dangers of illicit intercourse, and the education of the physician in the importance of early diagnosis and proper treatment. A national control with one broad strong policy has been advocated as necessary; but this is scarcely possible with our present political system except as a war measure. Though much may be accomplished by the measures outlined, syphilis or other venereal disease can not be stamped out completely so long as there exists an ineradicable instinct as a cause for its existence. Next in importance to the adult carrier is the syphilitic prospective mother. Such women may be reached in various ways; but the largest number can be reached best by a larger use and more widespread distribution of prenatal clinics. It is generally agreed that adequate treatment of such a mother throughout the period of her pregnancy or even through the last 5 months of her pregnancy will usually result in the birth of a healthy, nonsyphilitic child. The shorter the period of treatment prior to birth, the more likely is the child to be syphilitic; but even the shortest periods of treatment are not without benefit. If such a mother has had inadequate or no treatment prior to the birth of her child, it is then desirable that the infant receive treatment at the earliest possible moment. Here again the largest number should be reached through postnatal or infant welfare clinics. Having diagnosed the family as syphilitic because of the infant, the future pregnancies of the mother should be protected by proper treatment of the parents. This can usually be done with full cooperation after proper explanations.

Since there is no reasonable hope of preventing syphilis, our greatest effort must be directed toward treating the disease early and well. In the case of infants the management must be in the hands of one who is not only expert in the diagnosis and treatment of this disease; but one who is also expert in managing infant nutrition. Such a need calls for a high standard of education, which fact places the burden of the syphilitic infant upon the medical schools and their associated hospitals and clinics used for instruction of students. Though there has been a steady improvement in the teaching of these subjects, there remains much to be accomplished.

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THE FOLLOWING-UP OF SYPHILITIC SUSPECTS*

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IN the course of the routine Wassermann test done on each patient in the Base Hospital of Camp Logan, Texas, it was found that 8.15 per cent gave a positive reaction.

This percentage has been drawn from a laboratory study at the hospital of 3704 cases, covering a period of five and a half months, and exclusive of all clinically syphilitic cases. In this number are included a few groups of cooks and the like, from the camp, upon whom Wassermanns were done.

It is recognized in this study that at times measles, malaria, mumps, smallpox and scarlet fever and even subjects apparently in normal health exhibit positive Wassermann reactions. Less than 1 per cent can be attributed to these causes in this series.

This finding of a notable number of blood-positive persons, carries a twofold obligation.

First: To the army, while in the army.

Second: To the individual who should certainly have the benefit of specific treatment upon sufficient evidence that he may have syphilis; and this obligation has even a broader significance than the personal advantage alone, for it includes the social, with its ramifications, all the way from those he may infect, to the posterity he may poison.

There is no reason to doubt that many of the army base hospitals have systems for this very purpose, by which they effectually follow these cases whose blood gives positive Wassermann reactions, and yet who lack immediate clinical evidence of syphilis.

At this time, however, the system which we have adopted here, to keep track of these cases, seems worth describing because of its unusual simplicity.

The control of this simple system depends on the manner of using and filing the small card form shown below, which is so printed, perforated and folded, that it can be typed in duplicate.

---

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BASE HOSPITAL, CAMP LOGAN, HOUSTON, TEXAS

....

From: Chief of G-U Service.
To: Surgeon, ...
(Through Military Channels)
Subject: Following-up Syphilitic Suspects.

1. ....while a patient in the Base Hospital had on ...., 191...., a *positive* Wassermann, without other signs of Syphilis.

2. You are hereby requested to have this man returned to the G-U Service of the Base Hospital at 10:00 a.m............, 191...., for another Wassermann test, *and bring this notice with him.*

- -

The laboratory in the course of its routine Wassermann tests carried out on all patients in the hospital, sends a list of those patients who have positive reactions, with their rank and organization, to the syphilis ward of the genitourinary service. In addition to this the ward surgeons are notified to send all patients found to have positive Wassermanns, with their records to the syphilis ward, as soon as they are physically well enough. These patients are then carefully investigated and examined. If any overlooked evidence of syphilis presents itself, this finding and the positive Wassermann constitutes sufficient grounds to start for that patient a syphilitic register and to begin treatment at once, or later if the condition of the patient makes that advisable.

In the absence of any history or signs of syphilis confirmatory of the positive Wassermann, the *card* is filled out and sent to the patients' organization surgeon who is thus requested to see that the patient returns on the hour and day prescribed; to be further examined and another blood taken for a Wassermann testing. This process can thus simply be repeated, and in this manner the syphilitic suspect may be followed clinically and serologically, as long as it seems necessary, and until in the opinion of the genitourinary service the man should either be freed from the suspicion of syphilis or he may be given a short course of antisyphilitic treatment with diagnostic intent, to see whether it may not change the blood reaction and prove a case, and justify a therapeutic course of treatment.

In case the patient is discharged to duty before the laboratory return has reached the ward surgeon, the genitourinary service is simply sent the evidence of the positive Wassermann finding, and as in the previous case, makes out the *card* for the man's return for examination and a further Wassermann.

The time allowed to elapse between these "follow-up" visits is about one month.

The simplicity of the method rests largely on the manner of filing these recall cards. This is done in the following way, in what may be termed the envelop calendar file. The duplicate card (the original having been sent off to the man's organization surgeon) is placed in an envelop with the date of that man's return written on the up-turned flap. It is then put in the filing box in its proper place according to its date. It can then be dismissed from the mind, for when the appointed day comes round, it will be found at the front of the file and routinely removed on that day.

In the event of the man's not returning as requested, the card can then serve as the text of a letter to the company commander of the surgeon.

It can thus be seen how readily this small card can control the situation, and an otherwise arduous task.

At no time more than the present, when the war seems definitely done, could it be more important to seek out the syphilitics and give them appropriate treatment, against the time the army is disbanded and these unfortunates are thrown back upon civil populations.

It is impossible to bring to a finish this short account of how the spirochete is pursued at this camp, without mention of the man who has inspired its beginning; for to Lieut.-Col. John M. Willis, the commanding officer of the Base Hospital, whose lively interest in every plan that spells progress in medical matters, the success of this system will certainly be due.

ARSPHENAMINE AND NEOARSPHENAMINE PLUS ADRENALIN

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INTRODUCTION

FROM the very beginning of the new era in the therapy of lues as opened up to us by the work of Ehrlich and Hata, unpleasant after-effects following injections of ''606'' and ''914'' began to be reported. In a number of instances these terminated fatally. After approximately eight years' experience with these drugs and their present day successors and despite the fact that a large amount of work has been done concerning these reactions, we do not as yet completely understand their etiology. We are, however, in a position to state that they are less frequent and generally speaking less serious than formerly. Such precautions as the thorough preliminary examination of patients, careful attention to dosage, adequate intervals between injections, extreme care in the preparation of the solutions employed, a strict asepsis of all apparatus, and lastly, careful observation of the after-effects, have all been of value in this connection. In spite of a strict observance of these measures, reactions will occur and then we are confronted with the problem of how they should be dealt with. Because of the prominence of the vasomotor phenomena in a large proportion of these reactions Milian conceived the idea of employing adrenalin in their treatment. His results have since been corroborated by others, and adrenalin is now a well-recognized agent in such emergencies.

It will be the purpose of this paper to emphasize the use of adrenalin in certain of the reactions following the intravenous injection of arsphenamine and neoarsphenamine. Before doing so, I shall briefly describe those conditions in which adrenalin has been used and also discuss the several theories as to their causation.

DESCRIPTION OF REACTIONS

Among the most frequently observed reactions is what Milian has termed the "nitroid crisis" because of its resemblance to what occurs following the inhalation of amyl nitrite. This condition is characterized by marked redness of the cheeks and ears. The lips assume a very bright red hue which may be tinged with violet. Sometimes this redness is succeeded by a cyanotic color. In a severe case of nitroid crisis there is swelling of the lips and tongue accompanied by conjunctival injection. A feeling of suffocation or air hunger is almost always present. A marked crisis may result in syncope. Nausea and vomiting not infrequently accompany such a reaction. In addition to the nitroid crisis which occurs during or soon after an injection so-called secondary crises have been observed. These do not appear until several days later. In mild reactions one may see only facial flushing but no edema, this would constitute an abortive nitroid crisis. A rapid thready pulse is almost always exhibited during these crises and the face may be covered with cold clammy perspiration. The picture is most alarming to the novice, but such an attack is rarely ever fatal. We have merely described some of the salient points of this type of reaction. For full details our readers are referred to Milian's writings.[1]

A rare but extremely dangerous reaction is what that same writer has termed "serous apoplexy." This corresponds apparently to what most clinicians have called hemorrhagic encephalitis. It has been claimed that those who develop this reaction usually exhibit a nitroid crisis at the time of injection. In cases of serous apoplexy all apparently goes well as a rule until the third or fourth day after the injection. At that time the patient suddenly shows signs of cerebral disturbance. He becomes extremely agitated and often develops more or less marked epileptiform seizures which may be tonic, or clonic or a combination of the two. Later coma appears and is usually followed by death within twenty-four to forty-eight hours after the onset of such an attack. The case described by Sauphar[2] is a good example of serous apoplexy.

The coma is usually associated with elevation of temperature and facial congestion. Stertorous breathing has been described as a very unfavorable sign and cases developing it are said to be hopeless in spite of any sort of treatment.

ETIOLOGY OF THESE REACTIONS

As a result of the successful employment of adrenalin in nitroid crises and serous apoplexy, as well as in certain cases of headache and diarrhea following intravenous administration of these arsenical preparations, Milian is of the opinion that adrenal insufficiency plays a large part in their causation. The vasodilator properties of these drugs in the presence of lessened adrenal activity lead to the production of these after-effects, especially the nitroid crisis and serous apoplexy. This latter condition he believes is caused by a similar mechanism acting upon the cerebral vessels. Autopsies performed on cases dying after salvarsan injections by Marschalko and Vezprémi[3] tend to confirm this view. They found disseminated punctiform hemorrhages throughout the brain. Microscopically, there was no evidence of necrosis, suppuration or softening. A marked cerebral edema causing separation of the nerve fibers was observed. The brain cells were apparently normal. Similar findings have been reported by others. It is only fair to state, however, that not all fatal cases have presented these changes. In postmortem examinations of eight fatal cases Warthin[4] found that death was apparently due in all of them to the toxic action of the arsenic upon the renal epithelium.

Ehrlich[5] has expressed his views as follows: "Milian of Paris has done a great service by discovering the significance of adrenalin in a number of salvarsan accidents. He showed that the accidents described by Hoffman and Jaffé and Meirowsky which developed immediately after the injection of salvarsan and were characterized by blue-red swelling of the face, lips, and eyeborders, by dyspnea, etc., may be completely avoided if adrenalin be injected before the salvarsan injection. He showed further that severe diarrhea and suppression of urine, threatening life, which occurred after salvarsan injection were cured by an injection of adrenalin. Supported by these observations Milian has by means of energetic adrenalin treatment saved an otherwise hopeless case of encephalitis hemorrhagica, in which on the second salvarsan injection the deepest coma ensued." Ehrlich believed that in cases of hemorrhagic encephalitis a salvarsan derivative which he called paraminophenyl-arsenoxide played an important role. The formation of this derivative is favored by all factors capable of causing a delay in salvarsan excretion, such as an overdose or the presence of renal disease. He concludes as follows: "But it seems probable that yet a third factor enters into the matter which is perhaps the most significant. The irritated vessels only undergo a dilatation of so colossal a character under the influence of the arsenical substance when the normal regulator of the vascular system, adrenalin, is present in insufficient quantities in the blood."

Leon Bernard[6] has compared cases of serous apoplexy to an acute adrenal insufficiency. This comparison is strengthened he believes by: (1) the similarity of symptoms in the two cases, (2) the well-known destructive action of arsenic upon the adrenals, which has been proved experimentally, and (3) the therapeutic value of adrenalin in such cases following salvarsan injection.

Schamberg[7] has stated that he believes the immediate vasoparetic reactive symptoms are due to traces of an unidentified impurity in the drug and not to arsenoxide.

Lereddc[8] is of the opinion that the nitroid crises are of chemical origin due to the solution injected and that idiosyncrasy has nothing to do with their causation. He believes that insufficient alkalinization of the product employed is of prime importance. In this manner a toxic monosodic compound is formed which acts upon the bulbar centers. He does not agree with those who believe that they are due to anaphylaxis. Regarding serous apoplexy he believes it is due to Herxheimer's reaction just as are most of the accidents following intravenous injections of the arsenical preparations under consideration.

Danysz[9] believes that vomiting, diarrhea, chilliness, headache, and temporary fever which appear a few minutes to several hours after injection, as well as the nitroid crises of Milian, are due to vasodilatation as well as the formation of a precipitate and its temporary arrest in the capillaries. He further believes that the rapidity of appearance of these crises and their degree of gravity depend upon the dose injected, as well as its concentration. When the dose is augmented, one increases the amount of precipitate. A sufficient alkalinization of these products prevents the appearance of nitroid crises and other accidents in persons in whom the average composition of the blood is normal. Danysz has compared death after arsphenamine to anaphylactic crises, resulting in the formation in the blood serum of the patients, from contact with the arsphenamine which has been injected, in the formation of insoluble precipitates as a result of the combination of the arsenical salt with the calcium phosphates in solution in the blood plasma. These precipitates form emboli in the capillaries. If they are redissolved as a result of the action of certain amino derivatives, the accidents rapidly disappear. If, on the contrary, these accidents are prolonged for several days or become more aggravated and result in epileptiform seizures and a fatal coma it is because the quantity of precipitates contained in the blood plasma is such that it can not be redissolved. Danysz concludes that thanks to the work of Charles Richet it has been recognized that the cause of these accidents is none other than the formation of a precipitate in the capillaries.

Geiringer[10] believes that the immediate reactions are caused by injecting the solution too rapidly.

Kaliski and Strauss[11] have expressed the opinion that the immediate vasomotor symptoms which in their experience did not as a rule appear until patients had received several injections, while resembling anaphylaxis, are due to the toxic action of the drug on the vasomotor system.

After having seen a number of cases of nitroid crisis not only in our own private and hospital practice but also in Milian's service we believe that his theory as to their causation is the correct one in many cases. This we have proved to our own satisfaction by giving adrenalin to these patients. In a series of 500 intravenous injections of arsphenamine [using the diarsenol, arsenobenzol (Dermatological Research Laboratories, Philadelphia) and arsenobenzol (Billon brands)] we have observed nitroid crises in approximately 3 per cent. Most of them occurred with diarsenol. In an early series of cases published in 1912 Milian found this reaction present in 5 per cent of cases. Since that time he has no doubt seen a decrease.

We have seen a nitroid crisis appear with the first injection so the anaphylactic theory can not be always invoked. These crises in our experience have varied from a slight facial flushing with a feeling of fullness beneath the sternum or precordium to extreme redness of the face, ears and neck with edema of the lips and tongue accompanied by marked air hunger and conjunctival injection. None of our cases exhibited syncope, but on three occasions marked prostration was complained of.

All the injections were given in a dilution of 0.1 grams of arsphenamine to 25 c.c. of plain freshly bidistilled water. About seven or eight minutes was the average time consumed in giving a 0.6-gram dose. Hence we do not believe that concentration of the solution or excessive rapidity of inflow were important factors. We always add 3 or 4 drops of 15 per cent sodium hydroxide after the solution has cleared and when in doubt resort to litmus paper. In spite of these measures reactions will occur and since those we have seen responded to adrenalin it is our belief that adrenal insufficiency is the determining factor in their production.

Not having seen an example of serous apoplexy we do not feel competent to express a decided opinion as to its etiology. Certainly in view of the results obtained in a number of cases one can not but be impressed with the effect of adrenalin therapy. To say that all such cases have that same basis would be too broad a statement, but certainly a considerable number are thus provoked. The theory of anaphylaxis so alluringly presented by Danysz and Leredde's belief in the Herxheimer reaction would both seem to possess strong points in their favor and they no doubt may cause such reactions. In this connection we must consider the Herxheimer reaction in a broader sense than that in which it was originally described. It is not merely a temporary visible aggravation of preexisting cutaneous lesions, but a general reaction with a marked cerebro-meningeal "lighting up" as a result of the action of the arsenical preparation upon the spirochete. The so-called Herxheimer reaction has been described as appearing within 24 to 36 hours after an injection. This would also require modification since serous apoplexy does not usually manifest itself until the third or fourth day following an injection.

ADRENALIN THERAPY

Among those who have found adrenalin of value in these conditions, besides the originator of this method, are: Pollitzer,[12] Ravaut,[13] Darier,[14] Committee on Venereal Disease Office of Surgeon-General U. S. Army,[15] Sergent,[16] Florand,[17] Sauphar, Berman,[18] Meddis and Sterling,[19] Wood,[20] Kaliski and Strauss, Schwarzman,[21] and ourselves.[22] Leredde although differing with Milian as to the production of the nitroid crisis and serous apoplexy suggests the use of adrenalin in those conditions.

In using adrenalin one should employ an active solution. It must be protected from the light since it readily undergoes oxidation. This is shown by the production of a reddish color. When this color becomes marked the adrenalin is of little value. Adrenalin can be subjected to boiling for a few minutes in order to render it aseptic. The usual solution of adrenalin hydrochloride 1:1000 is commonly employed and is the preparation hereafter referred to unless otherwise stated.

A good test for determining the quality of adrenalin is the following which we have found extremely useful. To 3 c.c. of adrenalin solution one adds a drop of 10 per cent ferric chloride solution. If the adrenalin is good, a greenish color soon appears which changes to red when it is heated. A deteriorated solution will not give this reaction.

DOSAGE

Milian recommends the following doses: By mouth 1 mg. (1 c.c. of a 1:1000 solution), subcutaneously 1 mg. and intramuscularly ½ mg. The last named requires a smaller dose because of more rapid absorption. Per os is easy but of uncertain value, and if several milligrams are thus given in a short space of time, vomiting may result. We have made but little use of this method but have given adrenalin in most cases into the glutei just as one would administer an intramuscular injection of an insoluble mercurial salt. The injection is given in two stages because if perchance the needle should rest in a blood vessel and the injection be given the effect would be extremely unpleasant perhaps even grave, due to the sudden deposition of such a dose in the circulatory current. The intravenous route has been recommended in cases of coma diluting 1 c.c. of adrenalin (1:1000) in 100 c.c. of normal salt solution. As a preventative agent we believe that 2 mg. will suffice in most "nitroid" patients. One mg. may be given intramuscularly ten minutes before the intravenous injection. In those presenting a marked nitroid crisis we have not hesitated in giving double that amount. It is quite striking to observe the effect of adrenalin in these cases. Patients who would otherwise present a crisis perhaps even before 20 c.c. of the solution had been injected can support the next one very nicely. Sometimes they complain of malaise or exhibit slight reddening of the cheeks. As a curative agent adrenalin will shorten a crisis, but we believe its chief use in nitroid crisis is as a prophylactic. Milian also uses it to prevent fever, headache, vomiting, and diarrhea. We employed adrenalin successfully in the cases of two patients who developed a marked serous diarrhea after each injection. In each of them 1 mg. intramuscularly just before the injection and a like amount by mouth in a little water on the following day was sufficient.

CASE REPORTS

In serous apoplexy larger doses have been given. Florand's patient became comatose on the third day after a second injection of neoarsphenamine 0.30 gram, given in concentrated solution. Within one hour he received 4 mg. intramuscularly (in 3 doses). Three hours later the patient was so improved as to take 1 mg. by mouth. He made an uneventful recovery.

Another striking case is that of Sauphar in which coma ensued on the third day after an intravenous injection of neoarsphenamine 0.20 grams. This patient recovered under large doses of adrenalin.

Wood's first patient was practically anuric for two days after an intravenous injection of arsphenamine 0.6 gram. Twenty minims of a 1:10000 adrenalin solution were injected subcutaneously and about 4 hours later a like amount of a 1:1000 solution was given by mouth. This dose was twice repeated. A large amount of urine was voided one hour after the second dose. Following an intravenous injection of 0.6 gram of arsphenamine his second case developed severe nausea and diarrhea, both of which ceased after the administration of adrenalin.

Milian has reported the case of a young soldier who received an intravenous injection of neoarsphenamine 0.45 gram. On the night of the third day thereafter he complained of a terrific headache and soon became comatose. He was given 2-½ mg. of adrenalin by mouth and one hour later 1-½ mg. (1 mg. subcutaneously and the rest intramuscularly) and recovered.

Sergent's patient presented symptoms resembling those of acute adrenal insufficiency, profound prostration, vomiting, weak pulse, subnormal temperature, cramps in legs and abdomen, etc., the day after receiving 0.30 gram of neoarsphenamine intravenously. Recovery was complete under adrenalin.

We do not know just how the adrenalin acts. A purely vasoconstrictor action is not all that it performs, perhaps a cardiotonic action also comes into play. Milian has found that ergotine, a good vasoconstrictor, does not possess the same efficiency in these cases. He states that hypophysine plus adrenalin is a good combination.

The best index to the action of adrenalin is the marked pallor which it produces by constricting the blood vessels. This "leuco reaction," as it has been termed, is well marked about the site of injection and also the face. It may be slight or intense, but the patient does not faint. When well marked this indicates that the dose has been sufficient.

A generalized trembling is not uncommon after an injection of adrenalin as are also tachycardia and increased arterial tension. These are not so important, however, as the leuco reaction. The site of an injection is usually somewhat painful for a day or so.

The subject of reactions following intravenous injections of these arsenical products is a large one. We have only endeavored to bring out some of the most important after-effects and to emphasize the importance of adrenalin which has in certain of them an effect well nigh akin to that of a specific.

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THE TREATMENT OF SYPHILIS AT THE OUT-DOOR DEPARTMENT, TORONTO GENERAL HOSPITAL

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THE regular routine treatment of syphilis under a special clinic was begun at the Toronto General Hospital in the fall of 1915. Previous to that date, each clinic took care of its own cases. In November, 1915, the Special Treatment Clinic was organized and all cases of a specific nature or suspected as such, were referred there, whether patients were seeking relief from the medical, surgical, eye and ear, or any of the several clinics at the Out-door Department. A special card was introduced giving a brief outline of the history, source of infection, and general or special symptoms, while on the reverse side are spaces for indicating the form of treatment, dosage, reaction to treatment, and result of Wassermann tests.

From November, 1915, to September, 1918, there have been 899 patients under treatment. Of these, only 90 presented themselves or were referred to the clinic, in the primary stages of the disease,—170 with the so-called secondary lesions, while 639 were either in the tertiary stage or the disease was latent without symptoms of any significance. From this it can readily be seen that our results would not be so satisfactory as if we received the bulk of patients in the early stages of the disease.

SUMMARY OF RESULTS

Primary stage, 90 cases		
Those remaining negative,	37	or 41%
Those remaining positive,	5	or 9%
Those alternating positive and negative,	3	
Those discontinuing treatment,	45	or 50%
Secondary stage, 170 cases		
Those remaining negative,	57	or 33½%
Those alternating positive and negative,	26	or 15%
Those discontinuing treatment,	87	or 51½%
Tertiary or later stages of disease—70 cases taken at random from reports, under observation 2 years		
Those remaining negative,	30	or 43%
Those remaining positive,	40	or 57%

If we contrast the cases in the primary and secondary stages of the disease who remained faithful to their treatment throughout two years, we find that the percentage of cures is as follows:

Primary cases.	82%
Secondary cases,	67%
Tertiary cases,	43%

In the above statistics, many of the cases of primary and secondary stages showing positive or alternating between positive and negative Wassermanns, are still under treatment, having been under our care only a short time. When these have received their full course, the percentage of cures in the early stages will far exceed 82 per cent and 67 per cent, respectively, as shown.

The method of treatment is by intravenous injections of the arsphenamine compounds, followed by intramuscular injections of mercury in the form of salicylate. Along with this, copious dosage of the iodides is given in the later forms of the disease as this is said to assist the action of the arsphenamine compounds or mercury by its absorbing action on deposits, thus allowing more effective action by the specific remedies. No arbitrary rule is followed in the number or amount of treatments given patients. In my opinion this would be folly, since it takes far greater dosage to cure certain patients than it does others. Moreover many patients tolerate large quantities of the remedies, whereas others exhibit reactions on very small amounts.

The question of reactions following the use of intravenous injections of arsphenamine compounds, has not been satisfactorily explained in many instances. During the administration of a dose the patient may flush suddenly, the pupils dilate, stomach feels bloated and a full, bursting sensation is felt in the head. From this the patient soon recovers. Or a most intense pain in the region of the kidney is sometimes felt and may last several hours. Others show wheals appearing all over the body, like a most intense urticaria, even while the dose is being given, while the lips and whole face become swollen and distorted, accompanied by a certain edema of the larynx. Captain E. J. Trow of the Base Hospital Staff, reports two cases showing a rash similar to measles with sore throat and a temperature of 102° to 104°, which came on immediately following treatment. They were isolated. The symptoms soon subsided and a further dose was given a week later with similar results. These reactions may result from a certain toxicity of the drug used and may frequently be avoided by changing to a different compound.

Treatment is kept up at the Toronto General Hospital until two or three consecutive negative Wassermanns are obtained or until the patient shows signs of having reached the limit of toleration for the drug. This is best shown by a slight reddening of the wrists and forearms. When this appears, the intravenous treatment should immediately be suspended or severe dermatitis may follow. This holds whether the patient has had few or many injections. This sign was disregarded in the case of C. B. and a further treatment given with the result that a most severe dermatitis set in, accompanied by an acute nephritis, which almost proved fatal and kept her bedridden for three months. One case had a mild dermatitis on wrists and forearms after three .45-gram doses of diarsenol; another after one .3-gram and one .45-gram dose had a rather severe dermatitis of arms, chest and neck. A. G. had seven .6-gram doses between September 15 and October 25, 1916, and developed a severe dermatitis by November 6. However, if the slight reddening of wrists and forearms is looked for and due regard paid to its significance, the severer forms of dermatitis will be avoided.

After two or three negative Wassermanns are obtained, treatment is abated and the patient is asked to report in one month for a further test. If the Wassermann is still negative, a further lapse of three months ensues, unless symptoms arise, and another test is made. In this way control of all patients is maintained up to at least two years. If during that time, the Wassermann test returns to positive, as frequently is the case, further treatment is immediately given. The Social Service Department operates in connection with the clinic and any patients failing to return in the specified time, are either sent a notice or visited by a member of the service. In this way all patients are kept under observation until finally dismissed.

Cerebrospinal syphilis in its different forms is treated in much the same manner as other forms unless it is seen to have negative results. In such cases, intravenous injections are continued but blood is withdrawn one hour afterwards, the serum prepared and reinjected intraspinally. Fairly good results have been obtained. Another method used is that of withdrawing 10 to 40 c.c. of spinal fluid immediately after an intravenous treatment. This seems to have precisely the same effect, only much less toxic, that occurs when the arsphenamine treatment is made into the spinal canal.

The whole treatment of syphilis is tremendously simplified if we can but get cases in the first or early stages of the disease. The future holds out hope of this as the various laws now governing the control of venereal diseases will result in patients seeking advice at the first symptoms of trouble. The many educative efforts and publicity now being shown towards the evils of so widespread an infection will surely result in fewer unfortunates covering up their early symptoms, but rather the great majority will seek immediate advice with hope of an early cure.

Too much significance should not be observed in laboratory tests for the diagnosis or cure of syphilis. Some patients do not show any lowering of infection, according to the Wassermann test, even though vigorous treatment is maintained throughout two years or even longer; but all symptoms or physical evidence of disease may have disappeared. Captain Trow reports a case of sore on the foreskin from which smears were taken and stained with India ink, with negative results. Not satisfied, he excised the sore, had it sectioned and stained according to Levaditi's method, with negative results. Nevertheless, in three months the patient exhibited all the signs of secondary syphilis with sore throat, rash, falling hair, etc. It is a good rule that "when in doubt regarding a sore, treat as syphilitic." No matter how early treatment is begun, the blood will sooner or later show a positive Wassermann—only to become quickly negative—in the large majority of cases of syphilis.

No deaths have occurred since the installation of the clinic which could in any way be traceable to treatment.

Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs, Arkansas.

WM. H. DEADERICK, M.D., EDITOR

SUPERINFECTION IN SYPHILIS.—Joseph V. Klauder, Philadelphia. The Journal of Cutaneous Diseases, 1918, vol. xxxvi, p. 519.

The subject of superinfection is an interesting one from a clinical point of view and should be considered in the diagnosis of a genital lesion containing the spirochetes when appearing in persons giving a history of having had the disease. If in such lesions the spirochetes are found in profusion and the Wassermann reaction is at first negative, later becoming positive, it is evidence in favor of the lesion being a primary sore, a reinfection; whereas, if the spirochetes are present in scanty numbers and the Wassermann reaction is positive at the time of its appearance, it is evidence of a superinfection. Genital lesions which the author has observed and regarded as the result of superinfection were papular-ulcerative and ulcerating type, with little or no induration. They were clinically not chancres. It is probable that many so-called second attacks of syphilis, or reinfection are instances of superinfection. There is nevertheless evidence that true second attacks of syphilis may at times occur. By a second attack should be meant the occurrence, twice in a patient's life, of a primary sore followed by secondary symptoms, and if this definition is accepted, the phenomenon would be rather rare. As Neisser points out, it means not only the patient has so returned to the normal as to react to the syphilitic virus like that of a non-syphilitic, but that he has lost any immunity which may have been conferred by his first attack. In the differential diagnosis of a genital lesion of the nature herein reported, besides reinfection and superinfection, the following possibilities should be considered: Ulcerative processes over foci of syphilitic lymphangitis on the penis may in rare cases simulate a recrudescence of the primary lesion; a mucous patch or an abrasion; in these, however, the spirochetes are present in large numbers; a localization of spirochetes at the point of lessened resistance from the result of trauma.

PATHOLOGY OF CONGENITAL SYPHILITIC DISEASE OF THE EAR.—J. S. Fraser and R. Muir, Journal of Laryngology, Rhinology, and Otology, January, 1917.

In the fetus and in infants the changes found in congenital syphilitic ear disease have been otitis media with involvement of the labyrinth in some cases through rupture of the annular ligament and invasion of the vestibule through the round window; delayed ossification of the labyrinth capsule, with abnormal narrow spaces; intrauterine meningitis in the region of the internal meatus and neuritis (small cell infiltration) of the eighth nerve; changes in the organ of Corti and in other parts of the membranous labyrinth and nerve apparatus, especially the spiral ganglion. In young children (one to seven years) there exists at present very indefinite knowledge of the changes occurring in the ears in congenital syphilis. From clinical observations it would seem that otitis media is common in syphilitic children but the middle ear symptoms are soon replaced by those of inner ear lesions, the catarrhal affections developing into conditions which clinically correspond to otosclerosis. It would thus appear that in young children suffering from congenital syphilis severe deafness may be due to a (syphilitic ?) otitis media going on to labyrinthine involvement. On the other hand, it is possible that the otitis media is caused by the usual organisms and that in the syphilitic child the labyrinth capsule has such a feeble power of resistance that para- and peri-labyrinthitis supervenes, or the window structures give way with resulting infection of the hollow spaces of the internal ear. In the "late" type of congenital syphilis, coming on gradually or suddenly between the seventh and thirteenth years, interstitial keratitis is invariably present and Hutchinson teeth in about 50 per cent of the cases. But thus far microscopic examination of the ears in such cases has been almost entirely negative. Various views have been put forward to explain this "late" form of congenital syphilitic deafness, as for example, (a) that it is due to a neurolabyrinthitis spreading from the meninges; (b) that it is due to an endarteritis and hemorrhages; (c) the theory already referred to, otitis media followed by para- and peri-labyrinthitis or by invasion of the labyrinth through the window. Cases can probably be brought forward in support of any of these views. The authors report in great detail the microscopic examination of the ears of a case of congenital syphilitic deafness and a summary of the changes found in the following: Chronic adhesive process in the tympanum; leucolysis of the malleus (and incus on the right side) to the external attic wall; invasion of the labyrinth capsule from the submucous tissue of the attic, aditus and antrum and lower part of the tympanum; marked changes (in the nature of a chronic osteomyelitis) in the narrow surrounding the labyrinth capsule;

erosion of the bony capsule of the labyrinth; filling up of the perilymph spaces of the canals, especially their convexities, by granulation tissue and compression or obliteration of the endolymph space in these regions; obstruction of endolymphatic aqueduct; great dilatation of the membranous labyrinth, especially of the utricle, saccule, vestibular end of the endolymphatic duct, basal and middle coils of the cochlea; formation of new connective tissue in the scala tympani; secondary degenerative neuritis of the nerve structures of the membranous labyrinth.

A Case of Syphilitic Fever.—E. Hasell Wright, Lieut.-Col., I.M.S., Civil Surgeon. Coorg. Indian Medical Gazette, 1918, vol. liii, p. 214.

Pyrexia, due to syphilis, may occur at any time during the secondary and tertiary stages, and almost invariably occurs prior to the outbreak of the secondary rash, and may be intermittent, remittent or continuous. But the most interesting, from a diagnostic point of view, is that occurring many years after the primary infection, and such a cause of any undiagnosed fever should be borne in mind. Syphilitic fever may be mistaken for: (1) malaria, (2) enteritis, (3) tuberculosis, (4) septic inflammation, (5) rheumatic fever. The above case was firstly mistaken for (1) malaria, and in some respects resembled, (2) enteritis and (3) and (4) septic inflammation and rheumatic fever, Malaria was excluded by the constant absence of the plasmodial parasite in the peripheral blood, and the others by a process of exclusion, absence of classical symptoms, and aggravation of symptoms on trial of appropriate treatment or their effect being trivial or noneffective. Malarial fever is very prevalent in Coorg, and such a case might easily be mistaken for that disease. What chiefly directed the diagnosis was firstly the pigmented patches over the shins and the conditions existing in the genital regions and groins, the absence of malarial parasites in the peripheral circulation, after repeated examinations, and the failure of quinine to affect the fever, as the patient himself acknowledged. The history given of the onset of the pigmented patches and their distribution was not at all typical, but the author has had many cases of a like nature and naturally his mind has leaned to a diagnosis of syphilitic fever.

Gummous Pelvic Cellulitis.—Castex Revista de la Asociación Medicá Argentina, 1918, vol. xxix, p. 84.

The patient was a man of thirty-two, Spaniard, peon in a textile mill, married. Chancre when twenty-two years old. Knows of no secondary manifestations. Wife healthy, has had but one child, also sound. Patient's chief trouble constipation dating from childhood and extreme, requiring constant use of drastics and enemas. Emaciation and pallor. For one year past crises of pain, relieved by deffecation. His constipation occasionally alternated with attacks of diarrhea. There were also troubles of micturition. In passing on this case the author believed that he had evidence of syphilis which was not acquired but congenital, which may have explained the absence of secondary manifestations of syphilis. These evidences were minor stigmata which jointly may have indicated syphilis of the congenital type. The assumption was that the patient was afflicted with a gummous cellulitis of the pelvis. The patient had never received any treatment and his disease was presumably active. No case of syphilitic pelvic cellulitis is on record with the exception of a possible one mentioned by Fournier in 1902. Physical examination showed the presence of a pelvic neoplastic mass and the ordinary tumors found in the male pelvis could apparently be excluded. The potential spaces of the pelvis seemed to be filled with this mass. The author abstained from a Wassermann and placed the subject on intravenous mercurial injections. The result was a gradual and steady disappearance of the mass and a return of the general health.

SYPHILITIC PERITONITIS.—M. Letulle, Paris Presse médicale, 1918. vol. xxvi, p. 477.

Syphilis attacks the peritoneum much more frequently than is imagined. Neither is there any ambigüity about the nature of the lesions produced, for these are quite characteristic. Hepatic cirrhosis is very common in hospital practice among both sexes and many of these patients have a positive Wassermann, or, in other words, the two affections have a tendency to associate themselves together. The author has tested 154 subjects with hepatic cirrhosis and has obtained 74 positive reactions. That is to say every other cirrhotic is a syphilitic. Not all clinicians accept this kind of proof. The author has now for years subjected these patients to an intensive intravenous mercurial treatment—which as a rule is very well supported—along with large and increasing doses of iodide and various arsenicals. At times the results are surprisingly good, as in a case of clinical cure in a year's time of a case of syphilitic cirrhosis of the liver and syphilitic aortitis. Unfortunately these subjects when they reach the hospital are apt to be all in physically and moreover suffering from high degrees of ascites. They can no longer tolerate an intensive cure and are moreover demoralised, failing to keep up treatment and tending to run after their favorite alcoholic drink. The per cent of good results in these advanced alcoholic cirrhotics is very small. From a different angle cirrhosis of the liver is an affection known to end not infrequently in spontaneous cure. Syphilis is known to play a decisive role in the ascites component so that in all ascites we must never fail to suspect syphilis and make a thorough investigation to find or exclude it. The presence of an alcoholic or tuberculous component should not by any means exclude the likelihood of syphilis. Since a Wassermann negative has a questionable significance every case of cirrhosis ought to be submitted to an intensive antisyphilitic cure.

SOME OBSERVATIONS ON LATENT OR CLINICALLY INACTIVE SYPHILIS IN THE CANAL ZONE.—Guy L. Qualls, M. C., U. S. Army. Proceedings of the Medical Association of the Isthmian Canal Zone, 1917, vol. x, p. 58.

From a total of 1,198 colored surgical patients, 908 showed no evidence of syphilis and did not give history suggestive of the disease; 297 showed active evidence of syphilis or gave histories indicative of previous syphilitic infection. The Wassermann test survey shows 23.7 per cent of the nonsuspects to be syphilitic, and 36.7 per cent of the suspects to be syphilitic. A great total syphilitic infection of 27 per cent exists among all colored employees admitted to the surgical wards. The latent syphilitic infection among colored male employees in the Canal Zone is exceedingly high—23.7 per cent, as compared with the white employees showing 2.3 per cent. The total syphilitic infection among the white surgical patients is 15 per cent. The routine blood Wassermann test is an ideal to be attained in hospital practice.

FRAMBOESIFORM SYPHILIDE.—W. McMurray, Sydney, New South Wales. The Medical Journal of Australia, 1918, vol. ii, p. 306.

S. L., aged 49, a Dalmatian, residing in this country for the last fourteen years, gives a history of having coitus four months ago. There are two abrasions on the penis, one on the dorsum of the balanopreputial fold, and the other on the frenum. The glands in the groin are not affected, but the glands in the axilla are enlarged. On the chin there are three sessile tumors, the largest being the size of a shilling. Two partly coalesce and project abruptly about a quarter of an inch above the surface. The surface of each is light red color, granular and devoid of hair, except at the margin, where it is loose. The tumors have attained this size in six weeks. In the mouth at the commissure of the lip on the left side is an ulcerated surface and a mucous patch is present under the tongue. There are no other syphilides in any other part of the body. Spirochetes have been sought for, but none have been found. The Wassermann reaction is positive.

Some Remarks on the Relationship of Syphilis to Abortion, Miscarriage and Fetal Abnormalities.—Fred L. Adair, Minneapolis, Minn. The American Journal of Obstetrics and Diseases of Women and Children, 1918, vol. lxxviii, p. 687.

There were 1,095 cases in whom there was a history of 2,773 pregnancies, of which 2,422 ended at term. There were 109 cases who had 197 abortions in a total of 621 pregnancies or approximately one abortion to three pregnancies. In the nonsyphilitic and negative Wassermann group there were eighty-three cases with 142 abortions in 464 pregnancies, or about one to three. The thirteen syphilitic cases had twenty-three abortions in seventy-four pregnancies, or about one to three. Apparently syphilis is not a very potent factor in producing the termination of pregnancy during the first trimester. There were forty cases who had 62 miscarriages in a total of 202 pregnancies, or about one to three. There were thirty cases without evidence of syphilis in whom there were forty-nine miscarriages in 161 pregnancies, or nearly one in three. In seven cases with indications of lues there were ten miscarriages in twenty-seven pregnancies, or a little more than one to three. This indicates that syphilis is not responsible for any high percentage of miscarriages. When we consider the premature births in this series we find about one-third of the mothers giving evidence of syphilis. About 20 per cent of the premature infants give positive evidence of luetic infection. About 10 per cent of the mothers who had stillbirths gave positive Wassermann reactions. Of the stillbirths in the hospital 12 per cent were proved syphilitic. Two of the malformed infants were born to syphilitic mothers. This is a higher ratio for those having syphilis than for those who did not. Syphilis was proved in two out of five cases of hemorrhage of the newborn.

The Clinical Display of Syphilis of the Nervous System.—Joseph Collins, New York. The American Journal of the Medical Sciences, 1918, vol. clvi, p. 377.

The most striking facts that the author's statistics set forth are: (1) syphilis of the nervous system constitutes about 25 per cent of the neurologist's work; (2) tabes and general paresis constitute about one-half of syphilis of the nervous system; (3) when syphilis invades the nervous system, the symptoms that result resemble so closely those of any disease of the nervous system that expert examination is necessary to detect it. The third of these statements requires some discussion, though it may be considered an elaboration of the obvious. In the table there are a certain number of cases of migraine, of trigeminal neuralgia, of poliomyelitis, of arthritis deformans, etc. The author is not attempting to prove that there is such a disease as syphilitic migraine or syphilitic poliomyelitis. An individual who has had syphilis and upon whose soma it has written its signature may have attacks of migraine, of trigeminal neuralgia, of poliomyelitis or any other disease without such disease being of syphilitic nature. When the physician attempts the interpretation of such a case he must decide for himself whether or not the disease which the patient then has is of syphilitic origin. The author's criteria are if there is no other attributable cause, and if the disease yields to antispecific treatment, he is suspicious that the disease is of syphilitic origin. When he discovers alteration in the cerebrospinal fluid, which is satisfactory evidence of an active syphilis in the central nervous system, his conjecture becomes a certainty. For instance, a patient who recovers from trifacial neuralgia under vigorous salvarsan and mercurial medication and whose serum and cerebrospinal fluid (Wassermann) becomes negative is considered by him to be a case of luetic tic douloureux. Syphilis of the nervous system may and often does cause the symptoms of practically every disease of the nervous system. The practical application of the conclusion is that no one can be sure that syphilis may not be an etiologic factor until after laboratory investigation has been done. Syphilis invades the nervous system and often disorders it without producing the most constant pathognomonic sign, namely, loss of circularity of the pupils and impaired response to light and shadow. The sure way of curing syphilis of the nervous system is to prevent it.

REPORT OF A CASE OF CEREBROSPINAL SYPHILIS.—Guy L. Qualls, M. C., U. S. Army. Proceedings of the Medical Association of the Isthmian Canal Zone, 1917, vol. x, p. 60.

The interesting points in this case are the negative blood Wassermann reaction and positive findings in the spinal fluid, together with normal reflexes. The x-ray findings also pointed to organic lesions at the pylorus. The sluggish pupils and paresthesia together with the history and gastric symptoms, would suggest spinal syphilis, yet a positive diagnosis would be untenable without findings in the spinal fluid, which showed the Wassermann two plus, cell count 95.

FISSURED TONGUE AS A SIGN OF SYPHILIS.—Dr. Gaucher. Annales des Maladies Vener, June, 1917.

Gaucher recognizes, in addition to the already described plicated or "scrotal" tongue of congenital syphilis, a less conspicuous condition in which the tongue shows merely a number of shallow fissures, the result of a mild grade of poisoning by syphilitic toxins. While often manifested in congenital syphilis, this condition is at least as frequently seen in acquired syphilis. In the congenital cases it is at times accompanied by other lingual changes of like origin, such as leucoplakia or geographical tongue, as well as by various other dystrophic manifestations in particular an abnormal spacing of the median superior incisors. The characteristic tongue fissures are best seen when the papillæ are smoothed down to the lingual surface by passage of the finger over the latter. The median fissure usually present is merely the normal medial furrow in an exaggerated form; but there are also irregularly distributed lateral fissures, some running into the median fissure and others independent of it, some straight and others curved. As a whole they run longitudinally, but may run transversely or obliquely. The fissures at the margins of the tongue are generally the deepest. There is no subjective disturbance, save exceptionally a slight tingling of the tongue upon indigestion of spiced foods or acid fluids. The condition is a certain indication of acquired or inherited syphilis.

DETECTION OF SYPHILIS BY EXAMINATION OF THE MOUTH.—G. Railliet. Paris Médical, November 17, 1917.

Examining 103 men, nearly all between the ages of thirty-five and forty-six years, for oral evidences of syphilis such as leucoplakia, hypertrophy of the buccolabial glands, the mammillary eminence on the internal aspect of the first upper molars, emphasized by Sabouraud, and the folded or fissured tongue surface, recognized by Gaucher as a sign of acquired or inherited syphilis, Railliet found one or more of these signs in no less than 76 of the series, only 27 men being completely free of them. In 49 men but one sign was present, while in 28, two or more of the signs were variously combined. The mammillary eminence was present alone in two subjects; folded or fissured tongue alone in 17; leucoplakia in 22 and hypertrophy of the buccolabial glands in eight. In general, these lesions were not more pronounced when combined than when present singly. Incidentally noticed in occasional cases where a congenital perforation of the vault of the palate, septal deviation in two cases, nocturnal headache in one patient, and a papilloma of the left commissure with enlarged glands in one instance. Enlarged epitrochlears, however, were in no instance met with. Expressed in percentage figures, leucoplakia was present in no less than 42.8 per cent of all men examined. Fournier ascribes 90 to 95 per cent of all cases of leucoplakia to syphilis. In the present series leucoplakia coexisted with the mammillary eminence in four cases, with the folded tongue in eleven, and with the fissured tongue in seven. The mammillary eminence was observed in 38.09 per cent of all the subjects, the folded or fissured tongue in 36.89 per cent and the enlarged buccolabial glands in 14.56 per cent. According to these figures nearly one-half the men examined were slightly or markedly tainted with syphilis. To be sure, in many instances the infection was present only in a highly attenuated form, many of the men examined declaring themselves to be fathers of healthy children born at term.

THE BARTLETT AND O'SHANSKY MODIFICATION OF THE WASSERMANN REACTION.—E. H. Ruediger, Bismarck, N. D. The Journal of Infectious Diseases, 1918, vol. xxiii, p. 533.

Since a reliable rapid method would be greatly appreciated by all who have to do these tests, this rapid method was compared with the method regularly used at the Bismarck Hospital. The Wassermann reaction as regularly done at the Bismarck Hospital may be considered perfectly safe because false positive results have never been observed. As compared with the regular method, the Bartlett and O'Shansky modification gives by far too many negative results.

WASSERMANN REACTION WITH GLYCEROLATED HUMAN SERUM TWO YEARS OLD.—E. H. Ruediger, Bismarck, N. D. The Journal of Infectious Diseases, 1918, vol. xxiii, p. 351.

Glycerolated serum two years old gave results almost identical with those given by the fresh serum. All serums had become somewhat anticomplementary but the anticomplementary property was destroyed by heating to 56° C. for 30 minutes. The result obtained with the Wassermann reaction was not affected by the second heating.

THE WASSERMANN TEST IN RELATION TO THE DIAGNOSIS AND TREATMENT OF SYPHILIS.—O. H. Foerster, Milwaukee. The Wisconsin Medical Journal, 1918, vol. xvi, p. 424.

In early syphilis during the period of cutaneous and mucous membrane lesions, a positive reaction is found in practically 100 per cent of cases. Some of these may remain positive indefinitely when untreated; others may gradually become negative even without treatment, after a period of years. In this early stage a negative reaction is of greater diagnostic significance than at any other period, and repeated negative results rule out syphilis conclusively. During the period of latency about 70 per cent of cases give a positive reaction, but this varies within wide limits and is dependent upon the amount of preceding treatment, the length of time that has elapsed since cessation of treatment, and upon the period of latency, whether early or late. It is in the latent cases especially that judgment in interpretation is required. Strong positive reactions in this period are indicative of syphilis even when the history of infection is not obtained. Many of these four-plus reactions are uninfluenced by any form of treatment and remain fixed as such for years without change in the patient's condition. In active tertiary syphilis about 75 to 85 per cent of cases give a positive reaction. When the lesions involve the skin a positive finding is conclusive. However, in some cases with circumscribed or limited tertiary lesions of the skin, the reaction is negative and can not be of aid in the diagnosis. In addition to its usefulness in diagnosis, the Wassermann test is a valuable guide to the effect of the treatment. In the early preeruptive period, while the reaction is still negative, prompt treatment may abort the disease. In these cases the subsequent persistence of the negative reaction indicates a cure. When a negative reaction has been obtained after adequate treatment, the test should be repeated every three months for a period of at least one year. A most important factor in the proper interpretation of the results of the Wassermann test for diagnosis and especially as a guide in treatment, is the question of antigens. When the amount of antibody in the serum under examination is small, as in old or vigorously treated cases, dependence on a single extract as an antigen may lead to false negative reactions, owing to lack of sensitiveness of this particular antigen. The reaction will be reported as negative, when actually spirochetal activity is still present. This is especially true of the alcoholic extracts of syphilitic liver in common use. Somebody has said that the laboratory should refine diagnosis. It appears to the author that in respect to the Wassermann test the tendency in many instances has been to blunt the clinical judgment of the practicing physician. Owing to his acceptance of the result of the Wassermann test as an unqualified "yes" or "no," he gradually has come to subordinate his best clinical judgment to the report from the laboratory. However, in the diagnosis of syphilis abundant opportunity still remains for the exercise of diagnostic skill and clinical ability, aided and guided by the intelligent interpretation of the results of the Wassermann test.

A POSITIVE WASSERMANN REACTION WHICH CHANGES TO A NEGATIVE AT THE TERMINATION OF PREGNANCY.—Maud L. Menten, Pittsburgh, Pa. The American Journal of Obstetrics and Diseases of Women and Children, 1918, vol. lxxviii, p. 519.

The blood of pregnant women giving an antepartum positive Wassermann, frequently shows a negative reaction when the postpartum blood is examined.

VALUE OF THE WASSERMANN REACTION.—Robert A. Lambert, Miriam P. Olmstead and Harold C. Stuart, New York. Medical Record, 1918, vol. xciv, p. 454.

A comparison of the serologic and autopsy findings at the Presbyterian Hospital during the past three years brings out the following facts: Among cases showing anatomic evidence of syphilis at autopsy 85.7 per cent had given during life a four-plus Wassermann with both alcoholic and cholesterinized antigens. Among 188 cases showing at autopsy no anatomic evidence of syphilis, 93 per cent had given during life a negative Wassermann with both antigens and 7 per cent doubtful reactions, one-plus, two-plus or three-plus with either antigen. These findings, in the author's opinion, warrant the conclusion that the Wassermann test, properly carried out, can be relied upon as an important aid in the diagnosis of syphilis.

THE STATIC LABYRINTH IN SYPHILIS.—J. W. Downey, Jr. Transactions American Otological Society, 1917, vol. xxiv, Part 2.

In a large proportion of syphilitic cases both divisions of the eighth nerve will be affected and, therefore, both the auditory and static labyrinth should be tested. Patients with acoustic neuritis of syphilis may hear the voice surprisingly well and may not complain of deafness until questioned; the tuning forks, therefore, offer the best means of correct diagnosis. The typical hearing defect is a shortening of the duration of perception by bone conduction, out of all proportion to the shortening of the duration of perception for the same fork by air conduction, the retention of good hearing for the low forks, with a loss of perception, or a reduction in duration of perception, for sounds of high pitch. As regards the static labyrinth the most characteristic reaction of syphilitic internal ear disease is a lowering and confusion of all the responses and this may vary from a totally dead labyrinth giving no responses to the cases showing all the normal reactions reduced in degree. Vertigo is absent or it lasts but a few seconds. Falling is not definite. The patient, if tested quickly after rotation, will past-point with one arm but not with the other, or will only past-point for a few inches or will past-point incorrectly. The responses may be intensified by increasing the stimulation; thus, nystagmus may be absent after ten turns in twenty seconds, but may become evident for a few seconds after ten turns in ten seconds. With the cold caloric test it may require much colder water to bring out the response. Furthermore it is apparently possible in these cases for one semicircular canal of the same ear to be more affected than the others, hence, we may get normal responses from rotation with the head in the upright position (horizontal canals) and abnormal reactions with the head forward (vertical canals) and vice versa. On the other hand, there may be increased irritability of the static labyrinth, evidenced by prolonged nystagmus, marked vertigo, and nausea. There may be crossed past-pointing, right arm to the left and left arm to the right after turning to the right, and vice versa, as well as reversal of past-pointing (both arms to the left after turning to the right, and both arms to the right after turning to the left.) The reactions in most instances point to the ear which is most involved and one ear is usually involved to a greater degree than the other, though both as a rule are implicated.

SOME POINTS IN THE DIAGNOSIS OF SYPHILIS OF THE NERVOUS SYSTEM.—James H. Lloyd, Philadelphia. The Archives of Diagnosis, 1918, vol. xi, p. 57.

The question sometimes arises whether it is ever possible or justifiable to base a diagnosis of nerve syphilis on one symptom alone. This question is perhaps most likely to arise where the iris is found involved, or again when the reflexes, particularly the knee jerks, or the Achilles reflexes, are affected. Is there such a thing as monosymptomatic tabes, in which, for instance, nothing is observed but an Argyll Robertson pupil? Such a thing in a patient with a clean history of syphilis, and positive (or even negative) laboratory reports, would raise a large question in the mind of a neurologist. The cases of cerebrospinal syphilis seen at Blockley during the past winter indicate that pupillary changes are very common, although these changes are not all of the Argyll Robertson type. The pupils in some cases are sluggish both to light and accommodation the type known as ophthalmoplegia interna. Along with this there may be inequality or irregularity, dilatation or contraction. His experience at Blockley would lead the author to believe that the type known as ophthalmoplegia interna, or something approaching it, is one of the most common of the ocular disorders. Various forms of ophthalmoplegia externa may occur in syphilis, as is well known, either in tabes or in the cerebrospinal form. As early isolated or prodromal symptoms, they are especially important. Progressive ophthalmoplegia has usually been held to indicate a central or nuclear origin, but it may possibly be due also, in some cases, to involvement of the nerve trunks in a syphilitic meningitis. It would not do, however, to deny the possibility, in other cases, of nuclear involvement due to endarteritis of the vessels supplying the nucleus. Primary optic atrophy, progressing to complete blindness, may appear in syphilitics. Of other cranial nerves the acoustic especially should receive attention, since a slight degree of deafness is to be detected very early. Preservation of the knee jerks and Achilles reflexes is not incompatible with a diagnosis of early or incipient tabes. It is difficult, or even impossible, in hospital practice to determine the exact time of the disappearance of the knee jerks in tabes. In the great majority of cases they have disappeared before the patient's admission. This is true also of the Achilles reflexes. Hence physicians fall into the way of assuming that their very early disappearance is a uniform rule; or that without the loss of the knee jerks there can be no tabes. But, as already said, tabetic symptoms in the pupils have sometimes been observed for a period of years before the reflexes were lost and the disease frankly declared itself. Nevertheless, such cases are very rare. The tendency today is to ascribe system diseases of the cord—even locomotor ataxia—to an essential meningitis, as Nageotto and others have claimed; but there is good authority for believing that this is not always so, and that the original seat of the lesion may be in the tracts, or the neurones themselves. There is, for instance, as already pointed out, a primary optic atrophy, but whether this is due to an original infection of the membranes, as some hold, is not yet fully demonstrated. Anyhow, these rather rare forms of lateral sclerosis present the clinical picture of a system disease existing in the lateral tracts, very much as tabes is a system disease of the posterior columns. In the absence of postmortem studies, which were not available in that series of cases, the writer can not indulge in dogmatic statements as to a meningitis; but the clinical type is one which is undoubtedly to be seen in syphilis of the nervous system. This fact suggests also the possibility that amyotrophic lateral sclerosis may, in some cases at least, be a form of spinal syphilis. Whatever the exact pathology may be—whether a peripheral neuritis, a meningitis about the roots, a poliomyelitis or a degeneration of neurones—the fact is apparent that syphilitic infection may cause a high grade of muscular atrophy. It has yet to be determined whether such muscular atrophy, due to syphilis, may occur in nontabetic cases, and whether muscular atrophy may constitute the whole clinical picture. We are bound to keep an open mind still as to the possible ravages of syphilis in the nervous system, for it is by no means clear that all clinical manifestations of the disease have yet been recognized. There seems to be no reason to suppose that the spirochetes may not invade exclusively that portion of the cord and nerves which we speak of as the neuromuscular portion, in other words, the motor neurones and the enveloping membranes of the anterior roots. Finally it is well to call attention here to the possibility of grave errors in diagnosis, especially by surgeons, in early or marked forms of tabes. Such errors consist usually in mistaking tabetic crises for the signs of surgical disease in some one or other of the abdominal organs.

NEUROSYPHILIS—ITS DIAGNOSIS AND ECONOMIC IMPORTANCE.—John A. Fordyce, New York. Journal of the American Medical Association, 1918, vol. lxx, p. 1028.

In the past decade much progress has been made in our knowledge of the nature, development, prognosis and treatment of neurosyphilis. The various types had been correlated with the serology of the blood and spinal fluid and a fairly firm foundation established on which to build in the future. By carefully observing the data now available, we may be able later to answer some of the questions which so deeply involve the patient's future health and the community's welfare. Some of these questions are the following: (1) Are the present criteria of cure all that are demanded to insure against a relapse of the infection? (2) Assuming that we have a negative blood Wassermann during a year after treatment is discontinued which remains negative after a provocative arsphenamine injection and that the spinal fluid is not infected, the following questions come up for consideration: (a) Can we assure the patient with certainty against recurrence? A mathematical reply can not be made to these queries, but up to this time we have seen no relapses in patients who have complied with the criteria in question. All the evidence favors the view that a serologic and clinical cure will remain permanent. It is always possible, however, for spirochetes to be hidden away in some of the tissues too few in number to produce the Wassermann reaction but which may be activated at some future time and produce tissue reactions. This possibility has been observed in syphilis of the eye and in arteritis of undoubted syphilitic origin. (b) Does freedom of the nervous system from infection in the first year with a positive blood Wassermann indicate that such infection can not occur later from an uncured focus? This question can only be answered when we carefully compare the data obtained from cases of early infection with future observations of such patients. All institutions and physicians should therefore preserve carefully all records, serologic and clinical, and compare them with those obtained in future examinations. Standardized methods of diagnosis and treatment (amount and kind) with results should be adopted and preserved in the form of a medical register like the one used in the medical department of the army.

HANDLING OF THE VENEREAL PROBLEM IN UNITED STATES ARMY IN THE PRESENT CRISIS.—William Allen Pusey, Chicago. Journal of the American Medical Association, 1918, vol. lxxi, p. 1017.

All of the methods of attack on the venereal diseases may be grouped into four classes: (a) Social measures to diminish sexual temptation. (b) Education in regard to venereal diseases. (c) Prophylactic measures against venereal diseases. (d) Medical care. Social measures to diminish sexual temptation divide themselves in two sorts of activities: (1) the repression of prostitution and of the liquor traffic, and (2) the provision of proper social surroundings and of opportunities for recreation and diversion. Lectures and exhibits and pamphlets for the soldiers in general serve a useful purpose, but they do not reach the soldier that is in most need of them. To reach the soldier in the way that is unfailing and that makes a real impression on him is through his company commanders —the men from whom he takes his orders, and to whom he naturally looks for guidance. In the program everything possible is tried to discourage prostitution. It is a part of the policy to stimulate activity in providing adequate care of venereal diseases among the civil population, to the end, for one reason, that the numbers of venereal disease "carriers" shall be reduced as much as possible.

There has been a very noticeable access of energy in the public care of venereal diseases as a result of the whole program that we have been considering. But the segregation of prostitutes and the regulation of prostitution in the Continental sense, that is, the examination of prostitutes, their certification and their toleration in definite districts have not been included in this program, because they have not been regarded as advantageous. The necessity for medical prophylaxis is instilled into the soldiers' minds. They are universally told that it is not a sure preventive of infection; that the sooner it is applied the more likely it is to be effective; and that after eight hours it is likely to be ineffective. The taking of it, if exposed, is a matter of army regulation. In the planning of the base hospital of each cantonment, full provision has been made for venereal diseases. It is a part of the policy of the Surgeon General that acute venereal disease shall be confined to the hospital until the acute infectious stages are past. This means that all cases of acute gonorrhea belong in the hospital and all cases of syphilis which have early active lesions.

SYPHILIS AND VENEREAL DISEASES AS A PUBLIC HEALTH PROBLEM.—H. G. Irvine, Minneapolis. Journal of the American Medical Association, 1918, vol. lxxi, p. 1033.

The program as proposed, and as put into force by the War Department, has already been proved a success by the fact that our armies now have the lowest venereal disease rate of any army in the field, and for weeks the rate of the expeditionary forces has been only about half that formerly averaged by our Regular Army. The program as proposed for civilians is along the same lines and is intended to be carried out in cooperation with the Army and Navy. There is every reason to believe that it will also be successful, particularly if it receives the support of the profession. There is a good opportunity for the private practitioner to show his desire to help by complying with all the rules and regulations and by doing as much individual educational work as possible. The specialist who does not enter the Medical Reserve Corps has an opportunity to serve at home by taking an active part in this movement, by lending his assistance with his special training, not only in working out problems, but by giving some time to dispensary work in his community. There is need for the federal government to come to the state's aid in the way of finances just as England has done, and such legislation is now before Congress. With this assistance, the work will go on much more rapidly. Emphasis should be placed on the educational work, particularly in the medical schools, as the people at large depend on the physicians for information concerning these diseases, and unfortunately the majority of the medical profession have little idea of the modern conception of sex hygiene or the public health point of view of the problems of prostitution and venereal diseases. This is due primarily to a lack of teaching of these subjects in the medical colleges. A well-rounded program for combating venereal diseases must take cognizance of every factor that enters into their spread. Any attempt to limit the work to any one field will fail, just as medical efforts at reducing venereal disease through attempted regulation of prostitution have always failed. In its last analysis we must agree with Surgeon General Gorgas that venereal diseases depend upon sex immorality for their spread; and until we do away entirely with immoral sexual relations, we can not do away entirely with these diseases.

An Efficient State Health Program Against Venereal Diseases.—H. G. Irvine, Minneapolis, Minn. American Journal of Public Health, 1918, vol. viii, p. 599.

Inasmuch as the call for this work has come directly from the federal government, it seems only fair that the federal government should provide funds to subsidize the state work on at least a 50-50 basis. This would assist more than anything else in offsetting what I have found to be the biggest stumblingblock in the entire program, namely, the securing of proper funds for carrying on the work. If every state that appropriates thirty or forty thousand dollars could receive another thirty or forty thousand dollars from the federal government, sufficient money would be available so that the state could in turn subsidize the local communities, or could itself place a number of dispensaries at advantageous points throughout the state. It would be easier then to secure necessary detention hospitals, additional physicians, nurses, social service workers, equipment, etc., which is necessary for the carrying out of the program. Emphasis should be placed on the educational work, particularly in the medical schools, as the people at large depend upon the physicians for information concerning these diseases, and unfortunately the majority of the medical profession have little idea of the modern conception of sex hygiene, or the public health viewpoint of the problem of prostitution, or venereal diseases. This is due primarily to lack of teaching of these subjects in the medical colleges.

Venereal Disease in the Thirty-Ninth Division.—Loyd Thompson, Hot Springs, Arkansas, and J. R. Bolasny, Detroit. Journal of the American Medical Association, 1918, vol. lxxi, p. 1294.

The venereal problem in the Thirty-Ninth Division is similar to that in other cantonments. There has not been the whole-hearted support of the citizens and authorities of Alexandria in minimizing the amount of venereal disease that has been shown in some cantonment cities. The venereal prophylaxis as administered in the Thirty-Ninth Division has proved quite efficacious in preventing venereal disease. The venereal prophylactic station in Alexandria under military control is to be established. The use of dichloramine-T is of advantage in the treatment of certain cases of gonorrhea and chancroid. The best method of treating early syphilis (primary and early secondary) is probably the daily injection of 0.4 gm. of arsphenamine for five days, repeating the course in one month, with weekly injections of mercuric salicylate to the point of salivation.

Congenital Syphilis and the Doctor.—J. M. Wallfield, New York. New York Medical Journal, 1918, vol. cviii, p. 279.

When the doctor has made a correct diagnosis and helped his patient to get well, he may consider his task accomplished, but from a sense of duty he must go deeper into the subject and take into consideration the future children which may be born to the syphilitic parents, and he must also have in mind the welfare of the community at large. The parents should be strongly urged to undergo treatment and to refrain from further procreation meanwhile, even if such advice does, to a certain extent, come in conflict with the religious and even civil interpretation of the law. The physician should try to disseminate, in his social circle, as much knowledge on the subject as possible, especially among the younger men. There are very few degenerates who would jeopardize the future generation for the sake of their own temporary sexual gratification. Wide publicity on the subject seems to be the best plan. Nineteen eighteen is intended to be the child saving year, and the pediatric societies should have special committees for the purpose of spreading information on congenital syphilis to the public through the general press, lectures, and other usual means. Above all, one thing is certain, the sooner the press frees itself from false and detrimental prudery and calls things by their own names, the better for our social structure.

The Technic of Intravenous Medication.—Ferdinand Herb, Chicago. New York Medical Journal, 1918, vol. cviii, p. 498.

The patient is placed upon the operating table with the upper body fairly well elevated and with the arm slightly slanting downward in the direction from the shoulder to the finger tips. In this position, a better filling of the vein is secured without interfering with the injection. Then the author applies the cuff, attaches the inflating bulb and manometer, disinfects the arm and puts on pressure. If the blood pressure is known— and it should be— the pressure may be raised immediately to this point; if the blood pressure is not known, the oscillations of the hand on the dial may serve as a guide. As they cease, just enough air is released to make them reappear. No hurry is necessary. There is no pain. The author gives plenty of time until the vessel is full and hard. Then the needle is introduced. As the blood begins to show, he makes connection with the glass cylinder containing the solution, releases the pressure of the cuff by opening the air valve and proceeds with the injection. The sphygmomanometer, thus used, improves and simplifies the technic of intravenous medication or of taking blood for the Wassermann test. It has proved to be of decided advantage over the plain rubber tube ordinarily employed. It obviates unnecessary pain and does away with guesswork.

Diagnosis and Treatment of Syphilitic Affections of the Acoustic Nerve, With Special Reference to the Use of Salvarsan.—George E. Davis, New York. The Urologic and Cutaneous Review, 1918, vol. xxii, p. 631.

The occurrence of focal reactions in the acoustic, facial or other cranial nerves during the course of salvarsan therapy, in syphilitic cases, is no incrimination of this remedy directly, but rather an indictment of the technic of administration. Either the dose has not been sufficiently large, else not repeated sufficiently often and continued sufficiently long to completely destroy all the spirochete pallida, particularly those in avascular foci—as nerve tissue, or in other foci or recesses difficult of access—as the cerebrospinal fluid. When properly given we may safely acquit salvarsan of producing neurotropic lesions, as "neurorecidives," but we can not emphasize too strongly that its safety and efficiency in preventing and curing such syphilitic lesions depend upon its timely and intelligent administration, controlled by repeated examinations not only of the blood but of the cerebrospinal fluid.

Apparatus for Administering Arsphenamin at Temperature of Blood.—S. R. Thompson, Charlotte, N. C. The Journal of the American Medical Association, 1918, vol. lxxi, p. 1652.

The apparatus consists of a glass container practically closed with a wooden cover to prevent the entrance of cold air. In the center is a regular arsphenamine graduate. In the air chamber around this there are three 10-watt incandescent lights and a thermometer, registering in centigrade and Fahrenheit. The lights may be attached or on separate switches. The rubber tubing, mixing jar, needles, etc., may be of any type desired. Before the injection is begun the solution in the rubber tube can be brought to the proper temperature by being allowed to run back into the graduate. Solution left in the apparatus will remain at the desired temperature, depending on the number of lights used.

THE MODERN TREATMENT OF SYPHILIS.—Philip Goldfader, New York. New York Medical Journal, 1918, vol. cviii, p. 408.

In treating a syphilitic, do not give a short course of intensive treatment, obtain a negative Wassermann, and then stop treatment. If treatment is discontinued at that time, the Wassermann will become positive in a few weeks or months. As in tuberculosis, the patient and the disease must be treated continuously until results are obtained. Our insane asylums are overcrowded, as the result of the former quick and early cures, and our clinics contain the remainder of the incapacitated victims of this insufficient and hasty treatment. Our aim should be to secure a negative Wassermann as early as possible and to keep it so. Then treatment should be continued for several months thereafter, and the condition of the blood should be examined by reasonably frequent blood tests to determine whether the negative reaction has remained unaltered. The duration of treatment is still a question of opinion. Formerly, under mercury alone, the duration was set down as two and a half years, but, today, we can be less definite in our statement. The patient should be under treatment and observation for at least three years. Following this limit of three years, the patient should still be under observation for two to three years, and have Wassermann tests made every three or four months. Those cases which remain negative are the hopeful ones, while a relapse may be looked for in those in which the serum reaction returns positive.

CURE OF A SYPHILITIC MENINGITIS BY ARSPHENAMINE AND MERCURY.—Irving M. Snow, Buffalo. American Journal of Diseases of Children, 1918. vol. xvi, p. 163.

Neither the parents nor the child had any symptoms of syphilis, hereditary or acquired. A fall on the head acted as a provocative agent, causing cerebrospinal symptoms in a case of presumably latent hereditary syphilis. This, of course, is not unusual. The lesion in the cerebrospinal meninges was probably a proliferative gummous leptomeningitis involving the cortex and spinal meninges; also in ependymitis with an increase of cerebrospinal fluid and some hydrophallus. The choked disks were due to intracranial pressure from fluid and not to a direct inflammation of the optic nerve. Optic neuritis is present in 40 per cent. Of cases of cerebral syphilis. Ophthalmologists tell us that a high grade choked disk is usually a simple edematous saturation and may exist without disturbance of vision or injury to the retina, subsiding under antisyphilitic treatment. If the process is allowed to progress, it may cause partial optic atrophy. In this case the course, increase and gravity of the brain symptoms were discovered and controlled by the oculist. Every case of supposed epilepsy should have the fundus and spinal fluid examined. The decompression and aspiration were followed by no immediate relief save that the lessening of intracranial pressure gave the cerebral circulation a little more freedom. The patient was very responsive to treatment: the acute symptoms lasted about three months. Mercurial inunctions were given every day for five months and arsphenamine at first every week; later every two weeks.

THE ADEQUATE TREATMENT OF SYPHILIS.—Joseph Kaufman, New York. American Medicine, 1918, vol. xxiv, p. 545.

Every case should receive intensive treatment immediately upon making the diagnosis. Every case of early syphilis should be kept under active treatment for at least two years, with short intervals between courses. Every case of latent syphilis should be treated if the spinal fluid is positive. If the fluid findings are negative, and the patient has not had sufficient treatment, the patient should be kept under the treatment as described. In the positive cases, intraspinal therapy must be given. The patient should be given long courses of mercurial injections, keeping the dose at not more than one grain, repeated every five to seven days. All of these patients should also receive iodides. Every case of tertiary syphilis should be given intraspinal treatment, associated with mercurial and arsphenamine injections and the internal administration of iodides.

THE TREATMENT OF SPLENOMEGALY WITH ANEMIA IN SYPHILITICS.—J. Eason, Captain R. A. M. C. (T). Edinburgh Medical Journal, 1918, vol. xxi, p. 267.

A case of splenic anemia is recorded in which the Wassermann test was positive and antisyphilitic treatment produced definite improvement. The Wassermann test remained positive. The results obtained from specific and surgical treatment are compared by reference to seven collected cases. The late result in one operation case is also noted. The rationale of the surgical treatment is briefly considered. Recommendations are made for the management of such cases of syphilitic origin simulating Banti's complex.

EXPERIENCE WITH FOERSTERS' OPERATION FOR GASTRIC CRISES AND SPASTIC PARALYSIS.—K. Kawamura and T. Kimura, Kyoto, Japan. Surgery, Gynecology and Obstetrics, 1918, vol. xxvii, p. 134.

On the whole Foerster's operation is so successful that it has been repeated with satisfactory results a number of times since. The results immediately after the operation are especially remarkable. In the authors' first case, vomiting and pain stopped entirely from the day following the operation, and with a normal appetite of a healthy person, the patient gained in weight daily. The results of their second case were also successful. A boy, who could not stand up at all before the operation, walked fairly well with crutches and especially well when led by the hand. But at times after the rhizotomy, paraplegia occurred, which later disappeared partially although not completely. As its causes, the following technical failures are enumerated: harsh treatment of the spinal cord, injury of small arteries resulting in hemorrhage into dural sac and disturbance of nutrition of the cord, excessive desiccation of the cord on account of a long-continued depression of the head with elevated pelvis. Therefore, if we are to give a final decision as to the results of the operation, it is necessary to observe the patient for a long time afterward. In Little's disease, the after-treatment of the patient is of supreme importance. The use of the plaster of Paris bandage, with its covering easily removable, suitable exercise, massage, electrotherapy, etc., should be continued for some time.

THE RELATIVE EFFICIENCY OF THE DIFFERENT MERCURIAL PREPARATIONS IN THE TREATMENT OF CONGENITAL SYPHILIS IN INFANTS AND CHILDREN AS DETERMINED BY A QUANTITATIVE ANALYSIS OF THE MERCURY ELIMINATED IN THE URINE.—Walter Reeve Ramsey, St. Paul, and Mildred R. Ziegler, Minneapolis, Minn. American Journal of Diseases of Children, 1918, vol. xvi, p. 305.

In infants and children, mercury, when given by the mouth, by inunction or intramuscularly, is excreted at least partly by the urine. In newborn infants and older children mercurial ointment when placed in contact with the skin, without any friction being used (protected and sealed by wax paper from being volatilized and inhaled), is taken up by the skin and excreted in the urine and continues to be excreted in the urine for a variable time after all treatment has been discontinued. By inunction (with rubbing) mercury is readily taken up by the skin and eliminated in the urine and continues to be eliminated for a considerable time. When one inunction is given, the maximum daily amount of mercury is usually eliminated during the following twenty-four hours, smaller amounts being eliminated for a variable time. Where continuous inunctions are given there is an accumulation in the system and considerable amounts are eliminated at intervals with only traces between. It is therefore probable that it is unnecessary to have mercury in contact with the skin, either with or without rubbing as often or as long as has been generally thought necessary. This, however, must be determined by further clinical investigation. Mercury salicylate suspended in oil and given subcutaneously continues to be eliminated in the urine in appreciable amounts for eight days, or longer, the daily amounts eliminated varying widely. It is therefore probable that a repetition of the treatment, not oftener than at intervals of eight days would be sufficient. Mercuric chloride by intramuscular method, a favorite method in congenital syphilis, continues to be eliminated for eight days or longer. In all cases in which mercuric chloride was used either by mouth or the intramuscular method, protein was found in the urine. Calomel, 0.016 gm. every two hours for four doses, and gray powder, 0.03 gm. every three hours for three doses, continued to be eliminated in appreciable amounts in the urine for as long as nine days; the maximum daily elimination usually occurred during the twenty-four hours following administration. It is therefore probable that the daily use of any of the mercurial salts in the amounts usually prescribed, is unnecessary and presumably harmful.

NEW INVESTIGATION INTO THE TREATMENT OF DEMENTIA PARALYTICA BY SUBDURAL INJECTIONS OF NEOSALVARSAN.—Schroder and Helweg, Copenhagen. Hospitalstidende, 1918, vol. lxi, p. 945.

In 1914 Monrad-Krohn reported good results from the use of salvarsanized serum in the metasyphilitic affections, or rather he first saw good results in tabes only, for no corresponding benefit was seen in paresis. At a later period he seems to have obtained positive results from serum injected directly into the brain through a trephine opening, thereby raising the question as to whether simple trephining or injection of an indifferent fluid would not have been attended with transient benefit. The authors took up the subject at this stage of the research. Trephine openings were made at the hair line in the temporal region. The total number of patients treated was nine. Subdural intracranial injections were combined with intravenous injections. In no case was there any complete disappearance, even temporarily, from the blood and spinal fluid of the Wassermann but there was at times a general weakening of the reactions and a certain amount of improvement clinically. Four patients died while under treatment; or it might better be said that because of their desperate condition the subdural injections were given in the hope of arresting it. In several cases pareses developed directly after injection. As in these cases the disease was rapidly progressing it was not easy to decide whether the treatment was the sole cause of the accidents.

BOOK NOTICES

(Books for review should be sent to Dr. W. H. Deaderick, Associate Editor, Dungan-Stuart Bldg., Hot Springs, Arkansas.)

GENITOURINARY DISEASES AND SYPHILIS.—By Henry H. Morton, M.D., F.A.C.S., Clinical Professor of Genitourinary Diseases in the Long Island College Hospital, Genitourinary Surgeon to the Long Island and Kings County Hospitals, etc. 807 pages. Fourth edition revised and enlarged with 330 illustrations and 36 full-page colored plates. Cloth $7.00. St. Louis, C. V. Mosby Company, 1918.

In the 144 pages of this work devoted to syphilis the author considers the subject from history to treatment. After a description of the progress of the disease through the primary, secondary, and tertiary stages, syphilis of the viscera, bones, and nervous system receives special treatment. Separate chapters are given to the clinical and the laboratory diagnosis of the disease, laboratory technic being given in detail. Practical descriptions of the newer intraspinous methods of treatment add to the value of the book. The author's experience in the treatment of tabes by intraspinous injections of salvarsanized serum has been that the clinical symptoms, including gastric crises, and the gait, improve. He agrees with most syphilographers that this method in the treatment of paresis has been disappointing. The interpretation of the Wassermann test and the standard of cure of the disease are sane. If it has been the author's aim to present to the profession a practical work, eliminating academic discussion, he has succeeded admirably. The section of genitourinary diseases embraces both medical and surgical, and makes the book indispensable equally to the syphilologist and the genitourinary surgeon.

A COMPEND OF GENITOURINARY DISEASES AND SYPHILIS.—By Charles S. Hirsch, M.D., Urologist to the Jewish Hospital and Mt. Sinai Hospital, Philadelphia. 347 pages. Third edition, revised, with 59 illustrations. Cloth $1.50. Philadelphia, P. Blakiston's Son & Co., 1918.

The third revision of the best known compend on the subject has been done judiciously. The serologic diagnosis of syphilis has been brought down to date. The author believes that the most sensitive antigen for the detection of syphilitic antibodies in the Wassermann test is the extract of lean beef heart fortified with cholesterin, and unless this antigen is very carefully titrated to determine anticomplementary or refractory tendencies, a weak or pseudoreaction may be obtained. It is therefore always advisable to use alcoholic extract of fetal syphilitic liver as it is more reliable. The author recommends that in performing the Wassermann reaction more than one antigen be employed. The technic of the various methods of intraspinous medication is given briefly and clearly. The author has striven to make more than a compend and has succeeded admirably. The work will be found of great value, not only to the student, but as a handbook for the practitioner.

REPORT OF THE SURGEON GENERAL U. S. ARMY TO THE SECRETARY OF WAR.—Washington Government Printing Office, 1918, paper, 735 pages.

The portion of this report dealing with venereal diseases has some interesting features. The total number of cases of admission to sick report for venereal diseases for the total enlisted men, American troops, of the year 1917 was 71,955. The total number of days lost in hospitals or at quarters on account of these diseases was 875,553, or 2,399 years. Of these, 1,415 years were lost from gonorrhea, 584 years from syphilis, and 400 years from chancroid. The importance of these diseases in producing ineffectives in the army is thus obvious. Not only is venereal disease commoner among colored than white troops in the United States, but the separate diseases are commoner in this order, chancroid, syphilis, gonorrhea. There is about two and five-tenths times as much gonorrhea among colored as white recruits. The drafted men show a higher incident of venereal disease than volunteers in the ratio of four to three. There is almost exactly twice the amount of gonorrhea among rural recruits that there is among urban recruits. This report based on large and accurate statistics will be of great value from the public health and social standpoint.

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Original Articles

STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. III*

The Red Corpuscle Suspension for the Wassermann Reaction. The Preservation of Red Blood Cells

By JOHN A. KOLMER, M.D., and CLAUDE P. BROWN, M.D.,
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(Received for publication, November 9, 1918)

WHILE considerable work has been done with the question of the red blood corpuscles best suited as the indicator antigen in the hemolytic system for the Wassermann and other complement fixation tests employing human serum, it would appear that the majority of laboratories are following the original technic in using sheep cells, although many employ human, ox, chicken or the red blood cells of other animals. The question rests primarily upon the presence of natural hemolysins in human serum for these erythrocytes and their influence upon the delicacy of the reaction; aside from this question other factors are to be considered and principally the difficulties encountered in the preparation of immune hemolysin for the reaction by injecting the cells into rabbits, goats or horses, the amount of complement serum required to complete the hemolytic system and the ease with which the cells may be procured. For example, powerful anti-sheep and anti-ox hemolysins are readily and easily produced by the immunization of rabbits and the amount of complement required in the hemolytic system thereby reduced, whereas powerful antihuman hemolysins are produced with difficulty and require more complement for the lysis of an equal number of red blood cells. The influence of natural hemolysins in human serum on the Wassermann reaction will be discussed in a separate communication and particularly in reference to the hemolytic system adopted for the proposed standardized technic; in this paper we wish to record and discuss experiments concerning the preparation of the erythrocyte suspension irrespective of the kind of blood employed.

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*Presented before the annual meeting of the Association of Immunologists, New York, May, 1917.

SCOPE OF INVESTIGATION

In the original Wassermann reaction five volumes of sheep blood washed three times with saline solution and made up to one hundred volumes with the same solution, was employed. At the present time various methods are used in different laboratories for the collection and washing of blood and in the preparation of erythrocyte suspension. We have sought to make comparative studies of these various methods, determine their influence, if any, upon the Wassermann and other complement-fixation tests and on the basis of the results recommend a technic aiming to standardize and stabilize this phase of the reaction, which has not attracted very much attention as a possible source of variation and error. Since it may be necessary for certain laboratories to attempt the preservation of blood for the purposes of convenience, necessity or economy, we have included a study of various methods of preservation in relation to their suitability for the Wassermann reaction.

Part I

RESULTS OF EXPERIMENTS BEARING UPON THE COLLECTION AND WASHING OF BLOOD AND PREPARATION OF ERYTHROCYTE SUSPENSIONS

1. *The Influence of the Method of Collecting Blood Upon the Erythrocytes.*—In collecting blood for the purpose of using the erythrocytes for indicator antigen, three methods are commonly em-

ployed, namely, (a) bleeding into a suitable vessel and defibrinating with glass beads or rods, (b) bleeding into an anti-coagulating fluid, and (c) breaking up coagula of blood and thereby liberating erythrocytes. The latter method is frequently used for securing human cells from specimens of blood submitted for the Wassermann reaction.

We have studied the bloods of persons, sheep and oxen collected at the same time, in the following ways:

1. In sterile mason jars followed by immediate defibrination with glass beads.

2. In 1 per cent solutions of sodium citrate in physiologic saline solution in proportion of one part of fluid to four parts of blood.

3. In 1 per cent solutions of sodium citrate in Locke's fluid plus ⅛ per cent gelatin in the proportion of one part fluid to four parts of blood. Rous and Turner[1] have found that the addition of gelatin affords protection to the cells and particularly to the erythrocytes of the dog, which are known to be quite fragile.

4. By breaking up coagula in saline solution until heavy suspensions of liberated erythrocytes were secured.

In each experiment one kind of blood was collected by these four methods and washed at the same time with the same saline solution; 5 per cent suspensions of the erythrocytes were prepared and used in titrations and Wassermann reactions in constant dose with the complement serum. The results of several experiments are summarized in Table I and the following conclusions were reached as based upon studies with *freshly collected blood:*

1. The method of collection has but very slight influence upon the resistance of the erythrocytes, provided the cells are washed one or more times to remove all traces of liberated hemoglobin and serum.

2. Cells secured by defibrination yielded the same results as those secured with an anticoagulating fluid.

3. Cells collected in plain sodium-citrate-saline solution yielded identical results with those collected in sodium-citrate-gelatine-saline solution. Rous and Turner have stated that the protective value of gelatin is much less evident with human and sheep cells than with dog cells owing to the higher resistance of the former; our experiments corroborate their findings, and in addition have shown a similar resistance of ox cells.

4. Cells collected by breaking up coagula are apt to require more washing to remove liberated hemoglobin and may be found somewhat

TABLE I

INFLUENCE OF METHOD OF COLLECTION OF RED BLOOD CORPUSCLES ON RESISTANCE TO SERUM HEMOLYSIS

SOURCE	METHOD OF COLLECTION	SUSP. WASHED CELLS	HEMOLYSIN	COMPLEMENT DILUTION	RESULTS OF COMPLEMENT TITRATION							
					0.02 c.c.	0.03 c.c.	0.04 c.c.	0.05 c.c.	0.06 c.c.	0.07 c.c.	0.08 c.c.	0.1 c.c.
Human	Defibrinated	5%*	2 units	40%	N.H.**	S.H.	M.H.	H.	H.	H.	H.	H.
"	Decalcified	"	"	"	N.H.	S.H.	M.H.	H.	H.	H.	H.	H.
"	Decalcified in gel. sol.	"	"	"	N.H.	S.H.	M.H.	H.	H.	H.	H.	H.
"	Clot broken up	"	"	"	S.H.	M.H.	M.H.	H.	H.	H.	H.	H.
Sheep	Defibrinated	"	"	10%	N.H.	N.H.	S.H.	M.H.	M.H.	H.	H.	H.
"	Decalcified	"	"	"	N.H.	N.H.	N.H.	S.H.	M.H.	H.	H.	H.
"	" in gel. sol.	"	"	"	N.H.	N.H.	N.H.	S.H.	M.H.	H.	H.	H.
Ox	Defibrinated	"	"	"	N.H.	N.H.	S.H.	S.H.	M.H.	M.H.	H.	H.
"	Decalcified in gel. sol.	"	"	"	N.H.	N.H.	S.H.	S.H.	M.H.	M.H.	H.	H.
"	Decalcified	"	"	"	N.H.	N.H.	N.H.	S.H.	M.H.	M.H.	H.	H.

*Human cells used in dose of 0.1 c.c.; sheep and ox cells in dose of 0.5 c.c.; water-bath incubations for one hour.

**N.H. = No hemolysis; S.H. = Slight hemolysis; M.H. = Marked hemolysis; H. = Complete hemolysis.

more fragile. As shown in Table I, cells collected in this manner required the same complement unit to effect complete hemolysis, but smaller doses of complement showed more hemolysis.

5. In collecting small amounts of blood, as human blood or blood from an ear vein of a sheep, it is better and more economical to use an anticoagulating fluid because all of the blood is thereby saved.

2. *The Influence of Washing Erythrocytes Upon Their Suitability for the Wassermann Reaction.*—The original Wassermann test called for three washings of the erythrocytes in physiologic saline solution and this practice has been adhered to almost universally. The purposes of washing are to remove all traces of serum and any hemoglobin liberated by mechanical or spontaneous disintegration of red blood corpuscles. It is necessary to remove all traces of serum in order to (1) avoid possible precipitin reactions; (2) to avoid possible anticomplementary activity of the animal's serum if the blood is more than a day old; (3) to avoid anaphylactic reactions if the cells are used for purpose of injecting rabbits at long intervals in the preparation of hemolysin and (4) to avoid erroneous Wassermann

reactions if human cells are being employed by carrying over serum with the corpuscles.

As shown in Table II, washing has, however, but slight influence upon the results of the Wassermann reaction if the blood has been *freshly* collected. In this experiment fresh defibrinated sheep blood was centrifuged and a 5 per cent suspension prepared of the unwashed packed cells; the remaining cells were then washed with five volumes of saline solution and a second suspension prepared and so on until a fourth suspension had been prepared of cells after three washings. All suspensions were used in titrating a hemolysin and in the conduct of Wassermann reactions with the same set of sera; the results have shown that with the unwashed cells the control may very occasionally show a slight tendency to inhibition of hemolysis and a weakly positive serum react somewhat more strongly. After one washing the results were similar to those after three washings.

TABLE II

INFLUENCE OF WASHED AND UNWASHED CORPUSCLES FROM FRESH BLOOD UPON SERUM HEMOLYSIS AND THE WASSERMANN REACTION

CELLS	HEMOLYSIN TITRATION*				WASSERMANN REACTIONS WITH + AND − SERUM			
	0.05 c.c.	0.1 c.c.	0.15 c.c.	0.2 c.c.	Positive Serum	Control	Negative Serum	Control
Unwashed	S.H.	M.H.	M.H.	H.	++++	−	−	−
Washed once	M.H.	S.H.	H.	H.	++++	−	−	−
Washed twice	M.H.	S.H.	H.	H.	++++	−	−	−
Washed thrice	M.H.	S.H.	H.	H.	++++	−	−	−

*Hemolysin diluted 1:2000; complement serum for two pigs diluted 1:20 and used in dose of 1 c.c. Corpuscle suspensions were 5 per cent and used in dose of 0.5 c.c.

With blood collected four days or more before the tests and kept in a refrigerator as defibrinated blood without a preservative, the results were somewhat different inasmuch as the serum occasionally becomes slightly anticomplementary and sufficient may adhere to the unwashed cells to interfere with hemolysis in the hemolysin titration and Wassermann tests, as shown in one experiment in Table III. These faults were more evident when 5 per cent suspensions of whole blood were used owing to the presence of a larger amount of serum.

When the human cells taken from the specimens of blood submitted for the Wassermann test are employed, it is necessary to wash them at least once with five volumes of saline solution to prevent carrying

TABLE III

INFLUENCE OF WASHED AND UNWASHED CORPUSCLES FROM OLD BLOOD UPON SERUM HEMOLYSIS AND THE WASSERMANN REACTION

CELLS	HEMOLYSIN TITRATION				WASSERMANN REACTIONS WITH + AND − SERUM			
	0.05 c.c.	0.1 c.c.	0.15 c.c.	0.2 c.c.	Positive Serum	Control	Negative Serum	Control
Unwashed	S.H.	S.H.	M.H.	H.	++++	±	±	−
Washed once	M.H.	M.H.	H.	H.	++++	−	±	−
Washed twice	M.H.	H.	H.	H.	++++	−	−	−
Washed thrice	M.H.	H.	H.	H.	++++	−	−	−

over sufficient positive serum to influence a reaction with normal or negative serum. The danger of error, however, is slight even though the unwashed cells of an active syphilitic person are employed. In experiments using 0.1 c.c. of 5 per cent suspensions of unwashed cells secured by defibrinating the bloods of active syphilitics yielding strongly positive Wassermann reactions and centrifuging once to separate the cells and serum, in Wassermann reactions with normal and Wassermann negative serums, it was only occasionally observed that some interference of hemolysis resulted, attributable to the presence of syphilitic serum adhering to the corpuscles. After one washing the cells behaved in exactly the same manner as after three washings provided that at least five volumes of saline solution were used in each washing.

The Washing Fluid.—Additional experiments employing different fluids for washing blood as 0.85 per cent sodium chloride in distilled water; plain Locke solution; Ringer solution and Locke-gelatin showed no apparent differences with sheep, ox and human blood; the simple physiologic saline solution yielded results equally as good as the latter solutions.

Relative Amounts of Blood and Washing Fluid.—In washing defibrinated blood best results in point of time required for the removal of free hemoglobin and serum were observed when at least three or more volumes of washing fluid were used with one volume of blood; larger amounts of blood may require four or more washings before the last trace of hemoglobin and serum have been removed, the latter being tested for in the supernatant fluid by the heat and acetic acid test.

During the process of washing the blood, the supernatant saline solution after the second washing should be free of hemoglobin; otherwise the cells are too fragile or the washing fluid is not isotonic.

3. *The Method of Preparing a Suspension of Washed Red Blood Corpuscles in Relation to the Wassermann Reaction.*—Considerable influence upon the results of serum hemolysis is exerted by the manner with which the hemolytic antigen is prepared of the washed cells. In some laboratories the washed cells are measured with a pipet and suspended in saline solution; in others the volume of washed cells is read off directly in the graduated centrifuge tube in which they were washed; the results vary according to the method of measuring the cells and according to the duration and speed of centrifugalization of the last washing. With hemolysin and complement titrations preliminary to the Wassermann tests, this factor of variation in the density of the corpuscle suspension is adjusted and consequently is of little or no importance in relation to the Wassermann reaction itself, but nevertheless worthy of some attention in relation to attempts toward standardization of the technic.

The strength and dose of the hemolytic antigen for the Wassermann test determined by the amount necessary to serve as a clear indicator of the results and in relation to economy with complement and hemolysin, is discussed later in relation to the hemolytic system; here we wish to record fundamental experiments of some practical bearing.

Influence of Duration of Centrifugalization.—The speed and duration of centrifugalization in the last washing of red blood cells exerts considerable influence upon the actual number of erythrocytes in a volume of suspension and upon the results of serum hemolysis.

The results of an experiment with sheep cells given in Table IV, show that suspensions prepared of cells centrifuged for ten minutes or less, contain fewer erythrocytes and require less complement to produce hemolysis, than suspensions prepared of cells centrifuged for thirty minutes. The variation is much greater between five and ten minutes than between ten and thirty minutes, owing to the fact that with high speed the great majority of cells are thrown down within the ten minute interval. In this experiment the suspensions were prepared by reading off the volume of blood in a graduated centrifuge tube; when the corpuscles are measured with a pipet the variation is still greater, as shown in the following experiment.

Table IV

Influence of Duration of Centrifugalization in the Concentration of Erythrocyte Suspension

DURATION OF CENTRIFUGALIZATION IN LAST WASHING*	SUSPENSIONS****	TOTAL CELLS PER 0.5 C.C.	RESULTS OF COMPLEMENT TITRATION**					
			0.5	0.6	0.7	0.8	0.9	1.0
30 minutes	2 to 3%***	290,000,000	S.H.	M.H.	M.H.	M.H.	H.	H.
5 minutes	5%	315,000,000	S.H.	M.H.	M.H.	M.H.	H.	H.
10 minutes	5%	455,000,000	S.H.	S.H.	S.H.	M.H.	H.	H.
30 minutes	5%	590,000,000	S.H.	S.H.	S.H.	M.H.	M.H.	H.
5 minutes	2.5%	190,000,000	M.H.	M.H.	H.	H.	H.	H.
10 minutes	2.5%	210,000,000	S.H.	M.H.	M.H.	H.	H.	H.
30 minutes	2.5%	335,000,000	S.H.	S.H.	M.H.	M.H.	H.	H.

*Speed about 3000 to 4000 revolutions per minute.

**Mixed sera diluted 1:20; each corpuscle suspension used in dose of 1 c.c.; antisheep hemolysin in constant dose of 2 units; water-bath incubation for an hour.

***Five volumes of whole blood in 95 volumes saline (original Wassermann technic).

****Prepared by reading off volume of cells in graduated centrifuge tube.

Additional experiments consisting in centrifuging for a fixed interval of fifteen minutes at varying speeds, have shown similar variations in the concentration of the corpuscle suspension, due to differences in the packing of the corpuscle mass.

Variation in Concentration of Hemolytic Antigen Due to Method of Measuring Corpuscle Mass.—In some laboratories the erythrocytes are washed in graduated centrifuge tubes and after the last washing the corpuscle mass is read off direct and suspended in sufficient saline solution to yield the desired percentage suspension; in other laboratories the saline washing fluid is pipetted off after the last washing down to the corpuscles and the latter removed and measured with a pipet in the preparation of a suspension. In the latter method the resulting suspension varies greatly in the actual number of erythrocytes present, according to the thoroughness and care with which the supernatant saline is removed and according to whether or not the pipet removes the upper or lower (more concentrated) strata of cells. In Table V are shown some of the results observed in a large series of experiments in which suspensions were prepared of the same sheep blood washed at the same time and in the same manner; invariably suspensions prepared by reading off the corpuscle mass in a graduated centrifuge tube and diluting with the necessary amount of saline solution to secure a 5 per cent suspension were more uniform, showed more corpuscles per cubic centimeter of

TABLE V

THE MEASURE OF ACCURACY IN THE PREPARATION OF ERYTHROCYTE SUSPENSIONS BY DIFFERENT METHODS AND INFLUENCE UPON SERUM HEMOLYSIS

SHEEP NO.	METHOD OF MEASURING CELLS FOR SUSPENSION	ERYTHROCYTES PER 0.5 C.C. OF 5 PER CENT SUSPENSION	COMPLEMENT TITRATION					
			0.5 c.c.	0.6 c.c.	0.7 c.c.	0.8 c.c.	0.9 c.c.	1.0 c.c.
1	In centrifuge tube	750,000,000	S.H.	M.H.	M.H.	M.H.	H.	H.
1	With pipet	350,000,000	M.H.	M.H.	H.	H.	H.	H.
2	In centrifuge tube	720,000,000	S.H.	S.H.	M.H.	M.H.	H.	H.
2	With pipet	255,000,000	S.H.	H.	H.	H.	H.	H.
3	In centrifuge tube	730,000,000	N.H.	S.H.	S.H.	M.H.	M.H.	H.
3	With pipet	315,000,000	M.H.	M.H.	H.	H.	H.	H.

*The mixed sera of several pigs diluted 1:20 used with 0.5 c.c. of each corpuscle suspension and 2 units of hemolysin; water-bath incubation for one hour.

suspension and required more complement for hemolysis, than suspensions prepared with a pipet with the usual amount of care.

Suspensions prepared with a pipet may, however, be quite uniform provided the last washing of the cells is conducted in a uniform manner relative to speed and duration of centrifugalization; in Table VI are shown the actual counts of ten suspensions prepared of the blood of ten different sheep secured in abattoirs at different times.

TABLE VI

THE MEASURE OF ACCURACY IN THE PREPARATION OF ERYTHROCYTE SUSPENSIONS AND INFLUENCE UPON SERUM HEMOLYSIS

SHEEP NO.	THE NUMBER OF ERYTHROCYTES PER 0.5 C.C. 5 PER CENT	RESULTS OF COMPLEMENT TITRATIONS**					
		0.5 c.c.	0.6 c.c.	0.7 c.c.	0.8 c.c.	0.9 c.c.	1.0 c.c.
1	320,000,000	S.H.	S.H.	M.H.	H.	H.	H.
2	280,000,000	S.H.	S.H.	M.H.	H.	H.	H.
3	380,000,000	S.H.	M.H.	M.H.	M.H.	H.	H.
4	308,000,000	S.H.	S.H.	M.H.	H.	H.	H.
5	302,000,000	S.H.	S.H.	S.H.	H.	H.	H.
6	305,000,000	S.H.	S.H.	M.H.	H.	H.	H.
7	305,000,000	S.H.	S.H.	S.H.	M.H.	H.	H.
8	345,000,000	S.H.	M.H.	M.H.	M.H.	H.	H.
9	378,000,000	S.H.	M.H.	M.H.	M.H.	H.	H.
10	344,000,000	S.H.	S.H	M.H.	H.	H.	H.

*Corpuscle suspensions prepared with a pipet measuring 1 c.c. washed cells suspended in 19 c.c. saline solution.

**Complement serum of two or more pigs diluted 1:20; same hemolysin used in all tests in dose of two units.

While great variations in the concentration of corpuscle suspensions (Table V) show an influence upon the complement and hemolysin titrations, *slight differences in the actual number of erythrocytes present in different suspensions do not produce apparent variation in the results of serum hemolysis* (Table VI). In these experiments the complement serum was diluted 1:20 and used in amounts increasing by 0.1 c.c. with a constant dose of hemolysin; under these conditions it would appear that a difference of at least 100,000,000 erythrocytes per cubic centimeter of suspension is required before a definite influence upon the results of a complement titration becomes apparent. The slight differences shown in Table VI in which with six of the suspensions the complement unit was 0.8 c.c. of a 1:20 dilution and in the remaining four was 0.9 c.c. are within the limits of experimental error due to reading the results as all of the latter were almost completely hemolysed at 0.8 c.c. and were so read by one or more other laboratory workers.

Variation in concentration of corpuscle suspension exerts little influence upon the results of the Wassermann test provided the same suspension is used in the tests as in the preliminary complement and hemolysin titrations, but chances of error are present if one suspension is used for the titrations and a second for the main tests unless both are prepared in the same manner; likewise if the hemolysin is used in a fixed amount depending upon the results of a previous titration, the complement unit will vary not only because of a possible difference in the activity of the complement serum but also on the basis of variation in concentration of the hemolytic antigen. This point has generally been overlooked in discussions upon the variation in the hemolytic activity of the serums of different guinea pigs. For these reasons it would appear advisable to employ a fixed and uniform method for the preparation of the corpuscle suspension; the method recommended measures the corpuscles in a graduated centrifuge tube because of the greater accuracy and uniformity attained.

4. *Concerning the Variation in Resistance of Erythrocytes of Persons and Sheep to Serum Hemolysis.*—Of further interest in reference to the erythrocyte suspension for the Wassermann reaction, is the question of possible variation in the resistance of the erythrocytes of different persons and lower animals to serum hemolysis, as presenting a possible additional factor of variation. Ottenberg and

Hopkins[2] have described considerable variation in the resistance of cells from different sheep, although Ottenberg[3] regards the range of variation as exerting but a minor role in the irregularities in the results of the Wassermann test.

Insofar as we could determine by complement titrations in doses commonly employed and using the cells of healthy persons and sheep, variation in results ascribable to variation in resistance of the corpuscles to serum hemolysis was somewhat doubtful. Our experiments on this point were conducted with groups of bloods of ten persons or sheep at one time, the suspensions being prepared in such manner as to secure uniformity in the actual number of erythrocytes per cubic centimeter and all used in titrations with the same complement serum. The results of one experiment with human cells are shown in Table VII; seven of the specimens were from healthy adults and the remaining three specimens from adults with syphilis in the tertiary stages, before antisyphilitic treatment was begun and presenting the appearances of robust health; a variation of 0.01 c.c. in the doses of a 40 per cent dilution of complement serum failed to show any differences in the resistance of the different suspensions, as with nine of them the complement unit was 0.05 c.c. and with one 0.06 c.c.

TABLE VII

CONCERNING VARIATION IN THE RESISTANCE OF RED BLOOD CORPUSCLES OF DIFFERENT PERSONS TO SERUM HEMOLYSIS

SOURCE	COLLECTION	RESULT ON COMPLEMENT TITRATION						
		0.02 c.c.	0.03 c.c.	0.03 c.c.	0.04 c.c.	0.05 c.c.	0.06 c.c.	0.07 c.c.
Healthy adult male	Decalcified	N.H.	N.H.	S.H.	M.H.	H.	H.	H.
Healthy adult male	Defibrinated	N.H.	N.H.	S.H.	M.H.	H.	H.	H.
Healthy adult male	Clot broken up	N.H.	S.H.	M.H.	M.H.	H.	H.	H.
Healthy adult male	Clot broken up	N.H.	S.H.	M.H.	M.H.	H.	H.	H.
Healthy adult male	Decalcified	N.H.	S.H.	M.H.	M.H.	H.	H.	H.
Healthy adult female	Clot broken up	N.H.	S.H.	M.H.	M.H.	H.	H.	H.
Healthy adult female	Decalcified	N.H.	S.H.	M.H.	M.H.	H.	H.	H.
Adult male syphilitic	Clot broken up	N.H.	N.H.	S.H.	M.H.	H.	H.	H.
Adult female syphilitic	Clot broken up	N.H.	S.H.	S.H.	M.H.	H.	H.	H.
Adult male syphilitic	Clot broken up	N.H.	S.H.	M.H.	M.H.	M.H.	H.	H.

*Red blood cells washed three times with saline solution and used in dose of 0.1 c.c. of a 5 per cent suspension; complement used in 40 per cent dilution; antihuman hemolysin in 2 units. Water-bath incubation for one hour.

With the erythrocytes of ten healthy adult sheep collected in the same manner during one morning at an abattoir, washed and suspended so as to secure suspensions of approximately similar concentration, the results of titrations conducted with the same complement serum diluted 1:10 in doses varying by 0.01 c.c., showed closely parallel results (Table VIII); with eight of the suspensions the unit of complement was 0.1 c.c. and 0.09 c.c. with the remaining two. Two additional and similar experiments employing the corpuscles of ten different sheep in each yielded similar results. Probably titrations with complement serum more highly diluted so as to give a series of closer doses would have shown more differences, but under the conditions described the resistance of the corpuscles from different sheep was closely similar.*

TABLE VIII

CONCERNING VARIATION IN THE RESISTANCE OF RED BLOOD CORPUSCLES OF DIFFERENT SHEEP TO SERUM HEMOLYSIS*

SOURCE	RESULTS OF COMPLEMENT TITRATION					
	0.05 c.c.	0.06 c.c.	0.07 c.c.	0.08 c.c.	0.09 c.c.	0.1 c.c.
Sheep No. 1	N.H.	S.H.	S.H.	M.H.	H.	H.
Sheep No. 2	N.H.	N.H.	S.H.	M.H.	M.H.	H.
Sheep No. 3	N.H.	S.H.	S.H.	M.H.	M.H.	H.
Sheep No. 4	N.H.	N.H.	S.H.	M.H.	H.	H.
Sheep No. 5	N.H.	S.H.	S.H.	M.H.	M.H.	H.
Sheep No. 6	N.H.	S.H.	S.H.	M.H.	M.H.	H.
Sheep No. 7	N.H.	N.H.	S.H.	M.H.	M.H.	H.
Sheep No. 8	N.H.	S.H.	S.H.	M.H.	M.H.	H.
Sheep No. 9	N.H.	N.H.	S.H.	M.H.	M.H.	H.
Sheep No. 10	N.H.	N.H.	S.H.	M.H.	M.H.	H.

*All cells secured by defibrination, washed three times and used in dose of 0.5 c.c. of 5 per cent suspension; hemolysin used in dose of 2 units; mixed sera of 3 guinea pigs diluted 1:10 as complement. Water-bath incubation for one hour.

When a sheep maintained for Wassermann work is bled too frequently or too profusely, an anemia may develop which may materially alter the resistance of the red blood corpuscles even when due precautions are taken to use suspensions containing the average number of erythrocytes per cubic millimeter of suspension. This has occurred twice in the experience of one of us. In laboratories using an antisheep hemolytic system it is customary to keep one or more sheep for complement fixation work; a few workers believe that best results are secured by using an immune hemolysin prepared with the blood of the same sheep as used for the hemolytic antigen.

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*One of us (J.A.K.) has recently found the cells of a sheep secured in an abattoir highly resistant to serum hemolysis inasmuch as a volume of these cells required between five and six times more complement to produce hemolysis in the presence of two units of hemolysin than required for average sheep cells. These particular cells were titrated against four different complement serums and two different hemolysins, and the high resistance to hemolysis proved striking and unique inasmuch as the phenomenon occurred but once among the bloods of more than two hundred sheep used in Wassermann work during the past two years.

One of us (J.A.K.) has used for several years the blood of sheep secured twice weekly from an abattoir for hemolytic antigen and for purposes of immunization, with entirely satisfactory results; so far as we can ascertain maintaining a sheep for complement-fixation work is only a convenience and by no means a necessity, provided blood can be conveniently secured from an abattoir at least once a week and even less frequently if the cells are preserved. Lyon[3a] has reported that blood obtained from an abattoir is as well suited for hemolysis work as the blood from a single animal.

Part II

RESULTS OF EXPERIMENTS BEARING UPON THE PRESERVATION OF HUMAN AND SHEEP BLOOD

For the sake of necessity, economy or convenience it may be necessary in certain laboratories to attempt the preservation of the blood used in the preparation of the hemolytic antigen. Two methods have been tried, although the great majority of workers prefer the use of fresh blood: (1) the formalin method of Bernstein and Kaliski[4] also suggested by Armand-Delille and Launoy,[5] consisting in adding 0.5 c.c. of formalin (40 per cent) to 400 c.c. of defibrinated blood (approximately 1:800 dilution of formalin) and (2) the method of Rous and Turner,[1] consisting in collecting blood in Locke's solution containing 1 per cent sodium citrate in the proportion of one part of blood to four parts of solution, washing three times in Locke's solution containing 0.25 per cent gelatin and preserving in Locke's solution plus 2.8 per cent saccharose.

Bernstein and Kaliski found that defibrinated sheep blood preserved with 1:800 formalin proved satisfactory for two months, whereas plain defibrinated blood was generally unfit for use after seven days; also that blood collected in a 1 per cent solution of ammonium oxalate as an anticoagulant, followed by the addition of formalin to 1:800, kept as well as defibrinated blood with the same amount of formalin. These investigators found that formalin in dilution as low as 1:200 was without effect upon the Wassermann reaction and that formalized cells could be used for the immunization of rabbits in the production of anti-sheep hemolysin. Experiments with citrated human blood with the addition of formalin to 1:400 dilution yielded satisfactory results over a period of four weeks.

Rous and Turner conducted the majority of their experiments with the blood of dogs, owing to the well-known fragility of these cells; human blood was found by them most resistant to mechanical and chemical injury and sheep blood next. They found that the addition of gelatin in at least ⅛ per cent to the fluid used in washing dog blood, served to protect the cells against mechanical injury and that the addition of saccharose to 2.8 per cent in Locke's fluid, aided as an excellent preservative.

Reimann (6) in a study of both methods with sheep blood found that formalized cells (Bernstein-Kaliski) were satisfactory for four weeks and that saccharose-preserved cells (Rous-Turner) were satisfactory from 21 to 25 days, when kept in sealed ampules. This investigator compared both methods of preservation against fresh sheep blood in complement and hemolysin titrations and in the conduct of 150-200 Wassermann tests. Douglas and Brigger[7] found that sheep cells were well preserved by the Rous-Turner method for at least fifteen days, their resistance gradually decreasing. In their experiments the cells were preserved better at 9° C. than at 20° C.

The Preservation of Blood in Locke's Solution and Modifications Thereof.—In our experiments human, sheep and ox bloods were employed. The solutions which were prepared with chemically pure compounds and distilled water were sterilized in an Arnold before use:

Locke's solution:		
Sodium chloride	9.2	grams
Sodium bicarb.	0.05	"
Potassium chloride	0.1	"
Calcium chloride	0.1	"
Water	1000	c.c.
Locke-sodium citrate solution:		
Sodium citrate	10	grams
Locke's solution	1000	c.c.
Locke-gelatin solution:		
Gelatin	2.5	grams
Locke's solution	1000	c.c.
Locke-gelatin-sodium citrate solution:		
Gelatin	2.5	grams
Sodium citrate	10.0	"
Locke's solution	1000	c.c.
Locke-saccharose solution:		
Saccharose	28.8	grams
Water	208	c.c.
Sterilized and added:		
Locke's solution (sterile)	750	c.c.

The specimens were prepared as follows for each series of experiments with the different bloods run directly into the solutions:

Lot 1: One part blood in four parts Locke-sodium citrate solution.

Lot 2: One part of defibrinated blood in four parts of Locke's solution.

Lot 3: One part blood in four parts Locke-gelatin-sodium citrate solution.

Lot 4: One part of blood in four parts of Locke-sodium citrate solution. Corpuscles washed three times with gelatin-Locke's solution and kept in thin layers in Locke's-saccharose solution.

Lot 5: One part of blood in four parts of 1 per cent sodium citrate in physiologic saline solution; cells centrifuged, washed once with saline solution and kept in centrifuge tubes in mass under saline solution.

The Preservation of Blood by Formalin.—Specimens of blood were also collected at the same time and treated as follows:

Lot 6: Five-tenths c.c. formalin (39 to 40 per cent) added to 400 c.c. freshly defibrinated blood; to 40 c.c. of human blood was added 0.5 c.c. of a 1:10 dilution of formalin (formalin 1.0 c.c.; saline solution 9 c.c.).

Lot 7: Blood one part in four parts of 1 per cent sodium citrate in physiologic saline solution. To each 400 c.c. of this citrated blood was added 0.5 c.c. formalin (0.5 c.c. of 1:10 dilution to 40 c.c. of human blood).

Lot 8: Plain defibrinated blood in a sterile mason jar (defibrinated with glass beads).

All specimens were kept in a refrigerator at from 2° to 4°C. and some at 8° to 10°C.; all were washed three times with physiologic saline solution before use and tested at intervals over a period of six weeks in complement titrations and Wassermann reactions; parallel tests were made using fresh blood. With sheep and ox cells, 5 per cent suspensions were used in dose of 0.5 c.c. and human cells in dose of 0.1 of 5 per cent suspension. The complement serum was diluted 1:20 except with the human system when a 40 per cent dilution was employed. The respective hemolysins were the same throughout and employed in doses equivalent to two units.

Wassermann reactions were conducted with positive serums and readings made immediately after the second period of incubation and again after standing in a refrigerator overnight, in order to further test the fragility of the respective suspensions.

In recording the results shown in Tables X to XIV the following symbols were used in the complement titrations: S.H. = slight hemolysis; M.H. = marked hemolysis; H = complete hemolysis. In the Wassermann reactions the plus signs: ++++ = 100 per cent inhibition of hemolysis; +++ = 75 per cent inhibition; ++ = 50 per cent inhibition; + = 25 per cent inhibition; – = no hemolysis (negative).

TABLE IX

AGE OF ERYTHROCYTES IN DEFIBRINATED BLOOD IN RELATION TO RESISTANCE TO SERUM HEMOLYSIS

BLOOD	TIME SINCE COLLECTION	APPEARANCE OF SALINE AFTER THIRD WASHING	TOTAL NUMBER OF WASHINGS	SUSPENSION USED	COMPLEMENT	COMPLEMENT TITRATION					
						0.03 c.c.	0.04 c.c.	0.05 c.c.	0.06 c.c.	0.08 c.c.	0.1 c.c.
Human	2 hours	Colorless	3	5%	40%	N.H.	N.H.	S.H.	M.H.	H.	H.
"	1 day	"	3	"	"	N.H.	N.H.	S.H.	M.H.	H.	H.
"	4 days	"	3	"	"	S.H.	M.H.	M.H.	H.	H.	H.
"	7 days	"	5	"	"	S.H.	M.H.	H.	H.	H.	H.
Sheep	2 hours	"	3	"	10%	N.H.	N.H.	S.H.	S.H.	M.H.	H.
"	1 day	"	3	"	"	N.H.	S.H.	S.H.	M.H.	M.H.	H.
"	4 days	"	3	"	"	S.H.	S.H.	M.H.	M.H.	H.	H.
"	7 days	"	5	"	"	M.H.	M.H.	H.	H.	H.	H.

TABLE X

THE KEEPING QUALITIES OF DEFIBRINATED SHEEP BLOOD IN REFRIGERATOR

DEFIBRINATED BLOOD*	HEMOLYSIS IN WASHING**		COMPLEMENT TITRATION***					WASSERMANN REACTION	
	First	Third	0.6 c.c.	0.7 c.c.	0.8 c.c.	0.9 c.c.	1.0 c.c.	Immediate Reading	After standing 24 hours
Fresh	None	None	S.H.	S.H.	M.H.	M.H.	H.	++++	++++
1 day old	Very slight	None	S.H.	S.H.	M.H.	M.H.	H.	++++	++++
3 days old	Very slight	None	S.H.	M.H.	M.H.	M.H.	H.	++++	++++
5 days old	Slight	None	S.H.	M.H.	M.H.	H.	H.	++++	+++
7 days old	Slight	None	S.H.	M.H.	M.H.	H.	H.	++++	+++
10 days old	Slight	Very slight	M.H.	M.H.	H.	H.	H.	++++	++
14 days old	Marked	Very slight	M.H.	H.	H.	H.	H.	++	+
20 days old	Marked	Slight	M.H.	H.	H.	H.	H.	++	+

*Kept at 8° to 10° C.

**Blood washed with 0.85 per cent C.P. sodium chloride in distilled water.

***Complement prepared of mixed serums of guinea pigs and diluted 1:20; titrated with two units of hemolysin and 0.5 c.c. of each 5 per cent suspension of blood.

In the tables the appearance of the supernatant saline solution after the first and third washings is recorded (as none, slight or marked) as a means of following the degree of hemolysis and resistance of the various cells in this manner; if some hemolysis was evident in the saline solution of the third washing, washings were continued until a colorless washing fluid was obtained, unless more than six washings were necessary, in which event the cells were discarded as being too fragile for further tests.

The results of our experiments are as follows:

1. Human, sheep and ox bloods yielded similar results in all experiments although sheep cells were probably somewhat less resistant

TABLE XI

RESULTS WITH RED BLOOD CORPUSCLES OF SHEEP PRESERVED AFTER VARIOUS METHODS FOR SEVEN DAYS

CORPUSCLES	HEMOLYSIS IN WASHING		COMPLEMENT TITRATION					WASSERMANN REACTION	
	First	Third	0.6 c.c.	0.7 c.c.	0.8 c.c.	0.9 c.c.	1.0 c.c.	Immediate reading	After standing 24 hours
Fresh	None	None	S.H.	S.H.	M.H.	M.H.	H.	++++	++++
Lot 1	Slight	Slight	M.H.	M.H.	H.	H.	H.	++++	++
Lot 2	"	"	M.H.	M.H.	H.	H.	H.	++++	++
Lot 3	"	None	M.H.	M.H.	H.	H.	H.	++++	+++
Lot 4	None	"	S.H.	S.H.	M.H.	M.H.	H.	++++	++++
Lot 5	Very slight	"	S.H.	M.H.	M.H.	H.	H.	++++	++++
Lot 6	" "	"	S.H.	S.H.	M.H.	M.H.	H.	++++	++++
Lot 7	Slight	"	S.H.	S.H.	M.H.	M.H.	H.	++++	++++
Lot 8	"	"	S.H.	M.H.	M.H.	H.	H.	++++	++++

TABLE XII

RESULTS WITH RED BLOOD CORPUSCLES OF SHEEP PRESERVED AFTER VARIOUS METHODS FOR FOURTEEN DAYS

CORPUSCLES	HEMOLYSIS IN WASHING		COMPLEMENT TITRATION					WASSERMANN REACTION	
	First	Third	0.6 c.c.	0.7 c.c.	0.8 c.c.	0.9 c.c.	1.0 c.c.	Immediate reading	After standing 24 hours
Fresh	None	None	S.H.	S.H.	M.H.	M.H.	H.	++++	++++
Lot 1	Marked	Slight	M.H.	H.	H.	H.	H.	++++	++
Lot 2	"	"	M.H.	H.	H.	H.	H.	++++	++
Lot 3	"	"	M.H.	H.	H.	H.	H.	++++	++
Lot 4	Slight	None	M.H.	M.H.	M.H.	M.H.	H.	++++	++++
Lot 5	"	Slight	M.H.	M.H.	H.	H.	H.	++++	+++
Lot 6	"	None	S.H.	M.H.	M.H.	H.	H.	++++	++++
Lot 7	"	"	M.H.	M.H.	M.H.	H.	H.	++++	++++
Lot 8	"	Slight	S.H.	M.H.	H.	H.	H.	++++	+++

TABLE XIII

RESULTS WITH RED BLOOD CORPUSCLES OF SHEEP PRESERVED AFTER VARIOUS METHODS FOR EIGHTEEN DAYS

CORPUSCLES	HEMOLYSIS IN WASHING		COMPLEMENT TITRATION					WASSERMANN REACTION	
	First	Third	0.6 c.c.	0.7 c.c.	0.8 c.c.	0.9 c.c.	1.0 c.c.	Immediate reading	After standing 24 hours
Fresh	None	None	S.H.	S.H.	M.H.	M.H.	H.	++++	++++
Lot 1	Marked	Marked	M.H.	H.	H.	H.	H.	++++	++
Lot 2	"	"	M.H.	H.	H.	H.	H.	++++	++
Lot 3	"	"	M.H.	H.	H.	H.	H.	++++	++
Lot 4	Slight	None	M.H.	M.H.	M.H.	H.	H.	++++	+++
Lot 5	Marked	Slight	M.H.	H.	H.	H.	H.	++++	++
Lot 6	Slight	None	S.H.	M.H.	M.H.	H.	H.	++++	++++
Lot 7	"	None	S.H.	M.H.	M.H.	H.	H.	++++	+++
Lot 8	Marked	Marked	M.H.	H.	H.	H.	H.	++++	++

TABLE XIV

RESULTS WITH RED BLOOD CORPUSCLES OF SHEEP PRESERVED AFTER VARIOUS METHODS FOR FOUR WEEKS

CORPUSCLES	HEMOLYSIS IN WASHING		COMPLEMENT TITRATION					WASSERMANN REACTION	
	First	Third	0.6 c.c.	0.7 c.c.	0.8 c.c.	0.9 c.c.	1.0 c.c.	Immediate reading	After standing 24 hours
Fresh	None	None	S.H.	S.H.	M.H.	M.H.	H.	++++	++++
Lot 1	Marked	Marked	0	0	0	0	0	0	0
Lot 2	"	"	0	0	0	0	0	0	0
Lot 3	"	"	0	0	0	0	0	0	0
Lot 4	Slight	Slight	M.H.	M.H.	H.	H.	H.	++++	+
Lot 5	Marked	Marked	0	0	0	0	0	0	0
Lot 6	Slight	Slight	M.H.	M.H.	H.	H.	H.	++++	+++
Lot 7	"	"	M.H.	H.	H.	H.	H.	++++	++
Lot 8	Marked	Marked	0	0	0	0	0	0	0

and more difficult to preserve than the human and ox blood; the latter was included because certain laboratories have found the use of an anti-ox hemolytic system necessary and satisfactory.

2. The temperature at which blood is kept, regardless of the method of preservation, exerts an important influence. Alternate freezing and thawing results in hemolysis, but blood kept at 2°-4°C. is better preserved than at 8°-10°C. and the higher temperatures are increasingly less favorable for preservation.

3. Plain defibrinated blood may be preserved at a temperature under 8°C. for at least ten days (Tables IX and X). After four days there was an apparent decrease in resistance shown by the lesser

amounts of complement required for complete hemolysis but the cells were satisfactory. After ten days spontaneous hemolysis was greater and the blood became darker in color and gelatinous in consistency. Defibrinated blood kept at 18° to 20°C. was generally unfit for use after five days.

4. Defibrinated blood or blood collected in an anticoagulant fluid, washed three times with plain saline solution and kept in a mass in centrifuge tubes under the saline solution of the third washing (Lot 5) at a low temperature, is usually well preserved for at least seven to ten days; after two weeks the cells are quite fragile, require more than three washings, yield a small complement unit, and in the Wassermann reaction tend to break down upon standing overnight.

5. Blood collected and kept in Locke-sodium citrate solution (Lot 1) and defibrinated blood kept in plain Locke's solution (Lot 2) and in Locke-gelatin-sodium citrate solution (Lot 3) in the proportion of one part blood to four parts solution, are generally quite fragile and dark in color in seven days. Lot 3 of each blood preserved with Locke-gelatin-sodium citrate solution, was somewhat more resistant than the cells of Lot 1 and Lot 2.

6. Blood collected, washed and preserved according to the Rous-Turner method (Lot 4), was found satisfactory for two weeks. After fourteen days the cells became more fragile; in eighteen days the saline solution of the first and second washings was tinged with hemoglobin, the complement unit was reduced and the cells underwent slight spontaneous hemolysis in the Wassermann tests after standing overnight (Table XIII). At the end of four weeks the cells could still be used but were quite fragile (Table XIV).

7. Formalized cells (Lots 6 and 7) were well preserved for at least fourteen days; after that time they became slightly less resistant (Table XIII) but usable up to the twenty-fifth day. After twenty-eight days (Table XIV) they were quite fragile, somewhat dark in color, required four or five washings, hemolyzed with a small complement unit and in the Wassermann reactions kept overnight, underwent considerable spontaneous hemolysis.

Preserved Red Blood Corpuscles for Immunization of Rabbits.— Bernstein and Kaliski found sheep corpuscles formalized after their method satisfactory for purposes of immunization in the production of hemolysin; likewise Rous and Turner have found saccharose-preserved cells satisfactory. We have successively immunized rabbits with human, sheep, and ox cells preserved after both methods, washed five to six times before injection. Our experiments have not been sufficiently extensive to warrant an opinion on the merits of preserved cells for immunization as compared with fresh cells, and principally owing to the well-known variation in hemolysin response shown by different rabbits. It is our impression, however, that cells preserved by the Rous-Turner method up to fifteen days are well suited for the production of anti-sheep and anti-ox hemolysin; the use of formalized sheep and ox cells preserved for a period of three weeks proved satisfactory but resulted in the production of less hemolysin with the same number of injections. Considerable difficulty was experienced in the production of sufficiently powerful anti-human hemolysins and perfectly fresh blood appeared to be the superior variety.

Methods for Preserving Red Blood Corpuscles for Wassermann Reaction.—Fresh blood should always be preferred for the Wassermann reaction and preserved cells used only in case of necessity. In our experience the following methods of preservation have been found simple and practical:

1. Plain defibrinated blood kept at a low temperature; a suitable jar supplied with glass beads or small pieces of glass rod and a cover is sterilized with dry heat and used for the collection of blood at an abattoir or by venupuncture of a sheep. After defibrinating by shaking, the whole is kept at 2° to 4° C., leaving the defibrinated blood with the fibrin clot.

2. Formalized blood after the method of Bernstein and Kaliski kept at a low temperature. Defibrinated blood collected as described, is filtered through a small wad of absorbent cotton into a sterile flask and 0.1 c.c. of pure formalin (39 to 40 per cent) added to each 80 c.c. of blood; or the blood may be collected in 1 per cent sodium citrate in physiologic saline or Locke's solution, in the proportion of one part blood to four of solution, and formalized in the same manner. For small amounts of blood a 1:10 dilution of formalin in physiologic saline solution (1 c.c. of formalin and 9 c.c. saline solution) may be used in amounts of 0.1 c.c. for each 8 c.c. of blood. This is the simplest and most practical method for the preservation of cells over a period of two to four weeks.

Preserved blood tends to become dark in color and the cells in-

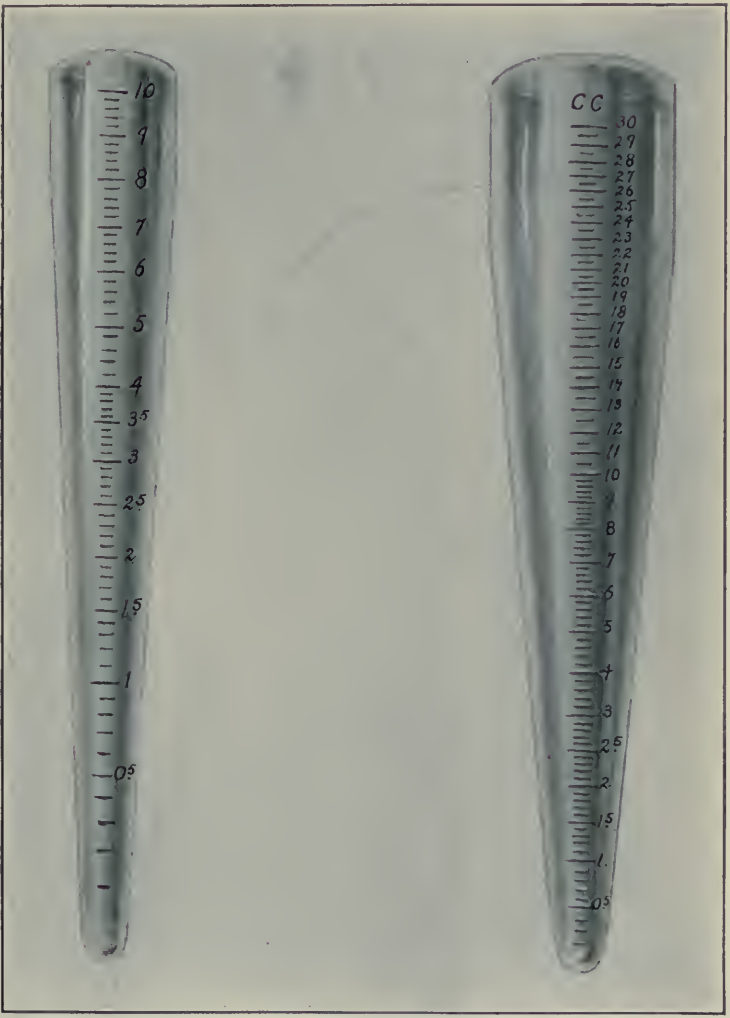

Fig. 1.—Special centrifuge tubes for the washing of blood for the Wassermann reaction, permitting the accurate measurement of the washed cells (original size).

creasingly fragile; it should not be used unless the following two conditions at least are fulfilled:

1. When washed with three or more volumes of physiologic saline solution by centrifugalization, there should be no discoloration of the supernatant fluid after the second washing.
2. The blood should become of a brighter and normal red color.

Part 3

TECHNIC OF PREPARING RED CORPUSCLE SUSPENSION FOR THE WASSERMANN REACTION

1. A satisfactory electric or water centrifuge should be available for washing the blood; the former is to be preferred. The instrument should be started and stopped slowly.

2. Washing the blood is best accomplished in accurately graduated centrifuge tubes. One of us (J.A.K.) has devised two sizes of centrifuge tubes which are especially recommended for this work (Fig. 1*). The smaller tube fits the ordinary 15 c.c. shield and is used for washing small amounts of blood when two cubic centimeters or less of massed corpuscles are required; the larger tube is made to fit the 50 c.c. shield of the International centrifuge and is used when larger amounts of blood are required. Both are graduated in 0.1 c.c. and permit of an accurate measure of the corpuscle mass after the final washing.

The centrifuge tubes may be sterilized prior to use, but this is not necessary; they should be chemically clean and rinsed with physiologic saline solution before use.

3. For washing blood physiologic saline solution is employed (0.85 per cent sodium chloride in distilled water).

4. In washing defibrinated blood, one volume of blood is placed in a centrifuge tube, two volumes of saline solution added and gently mixed; citrated blood collected in the proportion of one part blood to four parts citrate solution is used without further dilution. Each tube must be accurately counterbalanced in the centrifuge and whirled until all corpuscles have been thrown down, the time required depending upon the speed of the centrifuge (first washing).

5. The supernatant fluid is carefully removed down to the corpuscle mass with a capillary pipet (attached to suction pump or rubber

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*Made by the Edward P. Dolbey Company of Philadelphia, Pa.

teat) and at least three to five volumes of saline solution added; by capping the tube and inverting all the corpuscles are thoroughly but gently stirred and mixed in the saline solution and the tubes again centrifuged (second washing).

6. The supernatant fluid is again removed, replaced with saline solution, the corpuscles thoroughly mixed and again centrifuged for *twice as long* as found necessary to throw down the corpuscles in the second washing. This longer period of centrifuging is advisable to firmly and evenly pack the washed cells and *the speed and duration of centrifuging should be uniform in each laboratory as based upon experience with the particular centrifuge in use.*

7. If the supernatant fluid is discolored with hemoglobin the cells should be washed again until the supernatant fluid is practically colorless.

8. With the last washing the centrifuge is stopped slowly so as not to disturb the corpuscle mass, and *the volume of corpuscles read in the centrifuge tube before removing the supernatant fluid;* the latter is now removed and a suspension of proper strength prepared. A 5 per cent suspension, for example, is prepared by washing the cells from the centrifuge tube into a proper flask with nineteen times as much saline solution as corpuscle mass.

9. Sufficient corpuscle suspension should be prepared for the work at hand for the day, to obviate the necessity of preparing a second suspension and thereby introducing a possible source of error.

10. As the corpuscles in suspension tend to settle rapidly, the suspension should be *gently and thoroughly shaken* by hand before being used and *during the time of use,* if several minutes are required for pipetting the suspension; otherwise the doses will be uneven and inaccurate.

11. So far as practicable the suspension should be kept in a refrigerator when not being used.

12. Fresh suspensions should be prepared for each day's work of freshly washed blood, rather than carrying a suspension over for a day or more.

SUMMARY

1. With the fresh blood of persons, sheep, and oxen the method of collection by defibrination or in an anticoagulating fluid, had no apparent influence upon the red blood corpuscles insofar as their

suitability for hemolytic antigen in the Wassermann reaction is concerned.

2. Human blood cells secured by breaking up coagula in saline solution were slightly less resistant to serum hemolysis.

3. Small amounts of blood are best collected in an anticoagulating fluid.

4. Fresh blood cells should be washed at least once to render them suitable for hemolytic antigen; in the washing process at least three or more volumes of fluid should be used. Ordinary physiologic saline solution proved as suitable for washing cells as Locke's Ringer's and Locke-gelatin solutions.

5. The numerical concentration of a corpuscle suspension varies according to the duration and speed of centrifugalization in the last washing and according to method of measuring the corpuscle mass; best results are secured by measuring the corpuscles in an accurately graduated centrifuge tube after the final washing.

6. Variation in the numerical concentration of corpuscle suspensions may influence the results of serum hemolysis; for this reason the same hemolytic antigen must be used in the preliminary complement and hemolysin titrations as in the Wassermann tests, unless the suspensions are prepared with uniform accuracy.

7. The fresh erythrocytes of different healthy persons and sheep were found quite constant in their resistance to serum hemolysis. The use of suspensions of corpuscles from different persons and sheep does not constitute a source of error in the Wassermann test if technical conditions are correct.

8. Preserved blood may be used in the preparation of hemolytic antigen for the Wassermann test and for the immunization of rabbits, but fresh blood is always preferable. Preservation with formalin and saccharose solutions was found practicable for periods of two to four weeks; the formalin method is quite simple and to be preferred.

9. Methods for preserving blood and a method for preparing the red corpuscle suspension for a standardized Wassermann test are described.

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SYPHILIS IN SENILITY

Report of a Case

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IN the ever increasing literature appearing on the various phases of syphilis, but little contemporary reference can be found regarding the incidence of the disease in old age. The earlier literature also contains but scant reference to the subject.

The paucity of writing on the subject no doubt finds its explanation in the fact that fresh syphilis is but rarely seen at the end of normal sex life, and that the total number of such cases, sexually and accidentally acquired, is relatively small.

Some very excellent monographs are to be found in the French literature, notably in the contributions of Fournier, Quinquaud and Ullman, Renault and the French theses of Dulac, Regoby and Lebard. An extensive article on the subject is reported by J. Sigmund of Vienna, 1878.

As might well be expected, syphilis, as seen during the years of senility, presents a clinical picture differing from that seen in young adult life, dependent upon the obvious factors of lowered resistance and on the visceral and cutaneous changes incident to old age.

Except for Sigmund, who insists upon the relatively benign course of the disease in the aged, all other observers are agreed that in late life it is very apt to be more serious, not only in its local manifestations but also in complicating sequelæ.*

By far the largest number of cases reported are those of Sigmund, who after 30 years of observation, records 118 cases. Of these, however, 70, or almost ⅔ occurred before the age of 60 and many as early as 46. Other observers have taken a far older age as the lower limit, and it is quite certain that Sigmund's deductions, regarding the benign nature of the clinical course, were influenced by the fact that he included in his group patients in the prime of life.

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*"Si vous voulez avoir la verole, profitez au moins du temps on vous etes jeune, car il ne fait pas bon lier connaissance avec elle quand on est vieux." Ricord.

According to Renault, who up to his time carefully reviewed all the reported cases, the primary phase of syphilis in senile individuals is characterized first by a period of primary incubation longer than that seen in the young; a slowness in the evolution of the chancre and its induration, and finally a persistance and slowness of resolution, far beyond that which occurs in younger individuals.

The secondary period in general is said to differ, first in resistance of local syphilides to treatment; the marked tendency to recurrence; the tendency to precocity of lesions of a gummous type, and lastly the frequence of early nervous manifestations. In Fournier's group of 27 cases, 9 had severe nervous manifestations.

A large percentage of syphilis in senile individuals belongs to the interesting group of accidental infections and many of these cases for this reason are extragenital.

Since 1915 I have had four cases of syphilis occurring in senility under my observation and treatment. Their ages were sixty, sixty-two, sixty-four, and seventy-nine, respectively. Of these, all were genital infections, following coitus. Two were serious as evidenced by iritis in one, and iridocyclitis, glaucoma, and early central nervous involvement in the other. Three of the four cases, including one age seventy-nine, were sexually potent. The fourth acquired his infection during attempted intercourse, although he was impotent and had no libido. The oldest case, aged seventy-nine, has such striking clinical features, that it is deemed worthy of the following brief description.

Mr. S. E., aged seventy-nine, hotel porter by occupation, was transferred to my department at the University Hospital by the Department of Ophthalmology for an eruption on the scalp.

The patient had consulted the eye clinic for loss of vision of the left eye, due to glaucoma. The glaucoma was secondary to a specific iridocyclitis.

Family History.—Unimportant.

Past History.—Patient has always indulged freely in coitus since his early manhood. He never contracted gonorrhea and up to the present illness never had a penile sore. He maintains that his libido is just as strong as it ever was.

Present Trouble.—In June 1918, he was exposed (puella publica). Four months later, that is, early in October, a painless lesion appeared on the penis. Early in January a generalized eruption appeared on the body. The patient has had no headaches and except for his eye condition he has felt perfectly well.

Status Præsens.—Patient is a well-nourished old man; musculature is well preserved. On the scalp there are a large number of typical papulosquamous syphilides. The entire body, as well as the face is covered with a papulosquamous exanthem. Papuloerosive lesions of the scrotum, indurated chancre of the under surface of the shaft of the penis, papuloulcerative syphilides of the right angle of the mouth; condylomata lata of the anus. There is no general lymphadenitis, but the inguinal glands are slightly enlarged. There are no nodes on the long bones. The liver and spleen are not palpable. The nervous system from superficial examination is negative. The Wassermann reaction on the blood is four-plus positive.

The patient was at once transferred to the syphilitic ward and during the course of the following day a lumbar puncture was made, as is done on all cases.

Notwithstanding the negative clinical findings the spinal fluid showed 132 cells, marked increase in albumin and globulin and a four-plus Wassermann reaction.

The patient remained in the hospital, under our observation until March 3, or about six weeks, during which time he received five injections of novarsenobenzol, varying from .2 to .4 and one injection of arsphenamine .1.

He suffered no reactions and the local lesions entirely disappeared. After the first injection the iridocyclitis and glaucoma rapidly disappeared and up to the time of his discharge no further eye symptom had manifested itself. He was discharged on March 4, with instructions to continue his treatment in the form of the inunctions and to return for observation in three months.

The incidence of iritis in senile syphilis is recorded as a very frequent complication. Lebard, in analyzing the reported cases, states that it occurs in one-third of all the cases. This percentage coincides exactly with the degree of involvement of the nervous system, as given by Fournier, 9 out of 27 cases. As noted above I have found it in two out of four cases.

The features of interest in this case, which merit its publication are: (1) the extreme age of the patient and the acquisition of the disease by coitus. (2) The long period of primary and secondary incubation. (3) The occurrence of glaucoma, due to specific iritis with rapid subsidence on treatment. (4) The associated early nervous involvement without apparent clinical symptoms.

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A NOTE ON THE PREVALENCE OF SYPHILIS AS FOUND IN ROUTINE CORONER'S AUTOPSIES

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(Received for publication, March 12, 1919)

IN seven hundred routine autopsies performed for the Coroner of St. Louis during the last six years, about two-thirds of all adult cases have shown gross lesions of syphilis.

While it seems unnecessary to emphasize the frequency of this disease, it is only by constantly bringing out such examples as the foregoing that we will be able to stimulate the doing of routine Wassermann tests and treating this disease with understanding vigor.

It may be stated in the beginning that this series of cases represents in a measure untreated (or little treated) and unsuspected syphilis. The great majority of the people passing through the Coroner's office are representative of the underworld. They include gangsters, prostitutes, the poor and ignorant dwellers of the slums, many of the colored race, but, on the other hand, there are a certain number of cases of sudden death that are handled by this office which reach into some of our best families. We would expect in this work then a higher incidence of lesions than would occur in autopsies performed in private hospitals, since we are dealing in the main with untreated syphilis.

Warthin, in routine autopsies at Ann Arbor over a period of two years, found syphilis present in one-third of all adult cases. This series included a certain number of known treated and clinically cured syphilis; a few cases of clinically active syphilis and a large number of cases in which syphilis was denied or not suspected. While it is difficult to draw definite conclusions from the material obtained from such widely diverging sources, it is not surprising to find a parallel of two-thirds of all cases syphilitic where the material is drawn mainly from the ignorant individuals of the slums and underworld, as compared with one-third of all cases showing syphilis when drawn from rather well-to-do people of rural communities who are supposed to be always under good medical guidance.

In the lesions of acquired tertiary syphilis, which form the subject of this paper, I am including only the more obvious gross lesions of the more important organs, such as cardiovascular syphilis, neurosyphilis, syphilis of the liver and gastrointestinal tract, and genitourinary tract. I might say in passing that in these autopsies bones, neck organs, and sometimes intestines and testicles were not always examined. The types of lesions may be classified as: vascular, parenchymatous, gummatous, and fibrotic; the latter illustrated by serositis, healed scars, and leptomeningitis.

Regarding the frequency of these lesions, gummata were rarely found. The best examples were in the brain (meninges) and a few were found in the liver and testes in this series. The radiating scars that are supposed to represent healed gummata were more commonly found than the gummata themselves. Lesions of the stomach, that could be definitely termed syphilitic, were also rare, but three different types of lesions were noted: (a) Cases of diffuse or butterfly scarring of the pylorus. (b) What might be described as obliterative gastritis with replacement of the mucosa by fibrous tissue. (c) Syphilitic ulceration which in one case was followed by phlegmonous gastritis and death from septicemia.

Intestinal lesions were rarely found and then only as strictures due to thickening of the large intestines or rectum (gummatous infiltration). Lesions of the kidney are also rare, but there were a certain number of cases in which was found what could be considered a syphilitic nephritis. These cases were in young men in whom other active lesions of syphilis were present.

In the liver, aside from gummata, there were found many cases of cirrhosis with great distortion and deep lobulation that is described as almost always the result of infection of the Spirochete pallida. A great number of cases of enlarged, congested, firm livers, such as have been described by Woolley as luetic, were found, but they have not been considered syphilitic unless other typical lesions were encountered in the same case.

In the lung only three cases which were typically syphilitic were found, but it is very easy to overlook syphilis of the lung unless there is a careful study of the cases with routine microscopic examinations.

In the nervous system particularly of the meninges, lesions were found with great frequency which are unquestionably syphilitic. In addition to the gummata, which have already been mentioned and which are usually found in the cortex connected with the pia and dura, there is very frequently found a condition which has been accurately described by LeCount, i. e., the syphilitic leptomeningitis. These lesions as described by LeCount include three main types of changes in the pia: opacity or turbidity; patches of fibrous thickening and discrete focal lesions. Cerebral hemorrhage has not been included in this series although there were a number of cases in syphilitics under fifty years that appeared to be the result of specific rather than nonsyphilitic arteriosclerosis. Among these were three cases of cerebellar hemorrhage.

It is in the heart and blood vessels, however, that the lesions of syphilis are most common and most destructive to life. Whereas many of the lesions previously described are simply adventitious findings the vascular lesions are apt to be the immediate cause of death, e. g., ruptured aneurysms, occlusion of the coronary artery, heartblock, myocarditis, etc.. The majority of deaths from these lesions were found in individuals between forty-five and fifty-five years of age.

Regarding the frequency of vascular lesions, Warthin states that mesarteritis occurs in the aorta of all known syphilitics coming to autopsy. Oberndorfer found syphilitic aortitis in 82 per cent of autopsies done on individuals who had acquired syphilis. It has been stated that 22 per cent of all heart cases that come to the clinician are syphilitic.

In regard to the aortitis, if an error is made in diagnosis by the pathologist, it is more apt to be against than for syphilis. Aortas presenting the macroscopic appearance of atherosclerosis may, on microscopic examination, show typical syphilitic aortitis. The typical picture of syphilitic aortitis (macroscopic) is too common to need repetition; briefly, it is a condition practically limited to the aortic arch and more particularly the ascending aorta, the lesions rarely extending below the diaphragm. There may be thickening or thinning of the vessel wall with loss of elasticity and hyaline change without much tendency to calcification or atheromatous change. There are peculiar linear and radiating contractions or longitudinal rugæ. In the heart the aortic valves show all variations of involvement. Another common finding in this class of cases is the wide varieties of heart lesions. Extreme fibrosis of the wall of the left ventricle, hypertrophy, rupture of the ventricle and aneurysm of the heart are frequently encountered. Any list of coroner's autopsies will show a high percentage of deaths from ruptured aneurysms. In the light of our present knowledge, we can say that nearly all of these aneurysms are syphilitic in their origin.

In conclusion it may be stated that this is in no sense more than a note on the material that has been in hand. It merely represents some casual observations from a large amount of material that is going to waste. It is hoped that in the future funds will be available for the establishment in St. Louis of a modern institution where this material can be properly studied and tabulated and help in a measure to solve such problems as are suggested here. Despite all the statistics at hand, we do not know how many people are syphilitics. Despite the great progress that has been made in recent years in the right direction, we are still undertreating syphilis.

The social and economic and medicolegal aspects of syphilis are too far reaching to neglect any source of material that will advance our knowledge of the diagnosis and treatment of this disease.

SYPHILIS IN THREE GENERATIONS—A CASE REPORT

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THE following report of a family of syphilitics—a child, her parents, and her maternal grandmother—will be given in the chronologic order of their clinical investigations.

THE CHILD

Mabel S., aged ten months, was brought to the University of California Hospital on June 14, 1918, to receive medical advice for her irritated mouth and her tender knees. She was born after a normal pregnancy, of apparently healthy parents. Her weight, 10 pounds at birth, and 12 pounds at 2 months, had increased only 2 pounds in the past eight months. She had been breast fed for three months; she was then given certified milk for a similar period, and finally Mellin's Food. No fruit juice could be given on account of excoriated lips. There was no gastrointestinal disturbance except constipation. Her lips had been sore since her second month, and her knees, somewhat troublesome for a short period during the preceding winter, were now swollen and very painful. The first tooth appeared at three months, she sat up at six months and, at her present age of ten months, stands unsupported and utters a few intelligible words. There had been an occasional coryza and a laryngitis the preceding winter, but never any snuffles.

Physical Examination.—The child is somewhat pale and underdeveloped and lies with knees flexed on thighs, which are rotated outward. The child is fearful when approached and utters a curious hoarse cry. The lips are much swollen and there are herpetiform eruptions at the corners. The mouth is held partly open, and deep fissures radiate to all parts of the circumference. The gums are thickened and show deep blue lines at the base of the teeth, and numerous small submucous hemorrhages. Three incisors are present, two of which have lost their enamel. Mucous patches are seen on the tonsils and anterior pillars. The heart and lungs are normal, the thymus not enlarged. The spleen can not be palpated. The knees are swollen and there are a few ecchymoses over the dorsum of the feet and the lateral surfaces of both ankles. She protests very much when the limbs are moved. There are no palsies or atrophies, and all tendon reflexes are present. The blood count and the urine examination showing nothing abnormal. Wassermann of the blood is triple positive. The x-ray of the femora and tibiæ presents a widening of the shafts with some periosteal thickening, the cortex being thin with a slight tendency to longitudinal striæ. There is some irregularity at the epiphyseal junctions.

The child was put on orange juice and fresh vegetables with gratifying results within the first week. The legs became much less painful and could be easily manipulated. Inunctions were given from the fourth day and after four weeks' stay in the hospital the mucous patches had disappeared and the mouth condition was much improved. When last seen in September, 1918, she had gained three pounds, was walking about, the lips showed only one or two small fissures, and her general health was excellent. The specific treatment has been faithfully carried out. The diagnosis of congenital syphilis was readily made from the clinical findings, the x-ray, and the positive Wassermann. Whether this was complicated by scurvy could not be definitely determined.

The parents did not know anything about the condition of their child until she was taken to the hospital and both consented to physical examinations to substantiate the diagnosis.

THE MOTHER

The mother, Martha S., is twenty-five years of age, of slender build and delicate in appearance. The family history will be given later. She has had measles, typhoid, malaria and pneumonia. No history of syphilis could be elicited. The physical examination is negative except for a triple positive Wassermann of the blood. Menstruation began at sixteen and has never been regular. She married at twenty-two, had two spontaneous abortions, one at three weeks, another at three months; the child Mabel is the result of the third pregnancy.

THE FATHER

The father, John S., is twenty-four years old. His family history is negligible. He denies lues. His general health has been good.

He is not alcoholic. The Wassermann is triple positive, otherwise the physical examination shows nothing abnormal.

THE GRANDMOTHER

The grandmother, Mary T., appeared at the Out-Patient Department some two months after her son, daughter and grandchild had been investigated, complaining of a swelling of the neck. By occupation she had been housewife, waitress, and laundry-worker. Her father died at the age of fifty-two of cirrhosis of the liver; her mother is living and well at seventy-two; two sisters have heart trouble; one brother is living and well; two brothers died in infancy, one of an accident. She was married twice. Her first husband, whom she married at the age of sixteen, was sexually immoral and died at the age of sixty-four of paralysis. By him she had three children aged thirty-seven, thirty-four and twenty-five. Her second husband is tuberculous. At twenty-nine, the year after she bore the mother of Mabel S., she had scarlet fever and in the same year she had a complete hysterectomy. A severe iritis appeared when she was forty-four years old and gout some years later. The only history of syphilis obtainable was that she "caught the disease from her grandchild." The enlargement of the neck has been slowly increasing in size. For some years there has been dyspnea on exertion; occasionally she wakes up at night with air hunger. For the past month there has been cough, palpitation, and swelling of the hands and feet.

Physical Examination.—The patient is a small, alert individual, with some cyanosis of the face and extremities. The neck presents a right-sided unilateral pulsating tumor about the size of a small lemon. The apex impulse is diffuse, the heart is not enlarged. The first sound at the apex is weak, the aortic second sound is much accentuated but no murmurs are heard. The pulses are equal, synchronous and regular, of small volume, averaging 80 beats per minute. There are no enlarged glands. The blood pressure 255-155. The abdomen is negative. A trace of albumin is seen in the urine. Wassermann + + +. The x-ray of the chest shows the heart somewhat flat, aortic in type with a marked dilatation of arch and descending aorta.

Clinical Diagnosis.—Carotid aneurysm; aortitis; syphilis.

The accompanying diagram is a graphic representation of the family history.

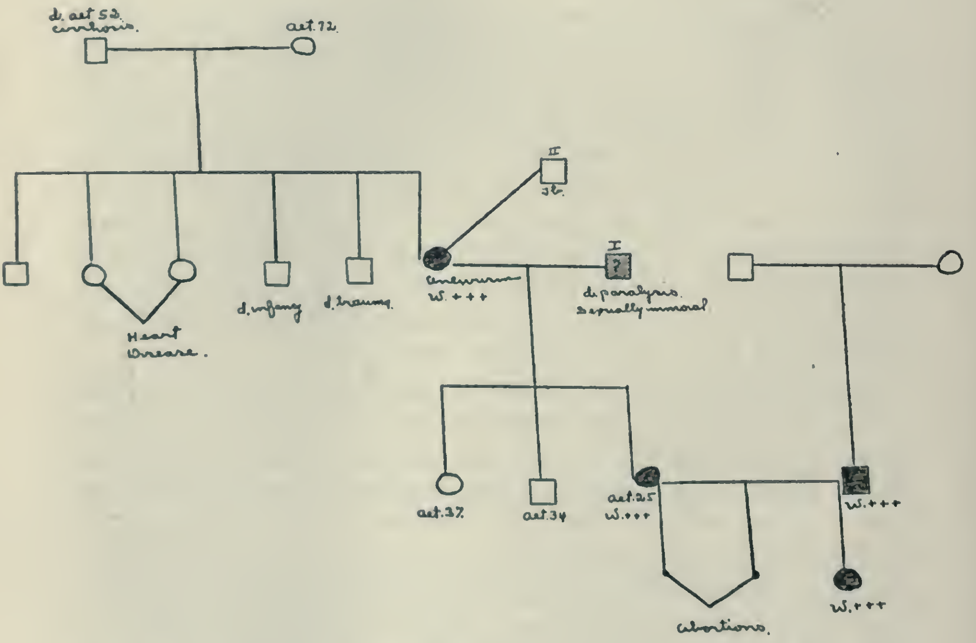
DISCUSSION

The consideration of this record of lues in three generations brings us face to face with some of the most obscure, as well as most disputed, points in congenital syphilis. An attempt to determine the hereditary manifestations in this particular group is, perhaps, a matter of some interest.

The grandmother, Mary T., had a very short child-bearing period, from her sixteenth to her twenty-ninth year, during which she bore to a man of low morality three children. There was a long interval of nine years between the second and the third. It is possible that infection with syphilis produced this interval. At the time that she bore her last child, the mother of Mabel S., she must have had grave pelvic disease, for in the year following this birth she underwent complete hysterectomy. As the aneurysm from which she is now suffering may be accepted as of syphilitic origin, and, as aneurysm is a late tertiary lesion, it is not improbable that her infection with syphilis took place during her early married life.

Our chief concern is, of course, her child, Martha S., the mother of the undoubtedly specific child. This woman has never shown any hereditary stigmata but she does give a positive Wassermann. Why is her Wassermann positive? Could she bear a specific child if her lues were transmitted to her by her mother as long as 25 years before? If this were possible, and if her lues were then virulent enough to infect her child so severely, should she not have infected her husband just as severely? He denies all knowledge of acquired lues, but his Wassermann is triple-plus. He may perhaps be the victim of hereditary lues. But the objections to this theory in his wife's case, would hold good in his. If we disregard his denial of acquired lues, it can be easily understood how he could infect his wife without her knowledge so far as demonstrable physical signs are concerned and how she could transmit the disease to their child (Colles' law).

It is possible to make further deductions and theorize *ad infinitum*. Transmission of syphilis in this family can not be proved. It would need stronger evidence than is here obtainable for us to accept this case report as an example of inherited syphilis in the third generation. Edmond Fournier has published numerous instances of "Syphilis héréditaire de seconde génération," some of which are no more convincing than this one. The grandmother has syphilis, her daughter has syphilis, the grandchild has syphilis; the father received his syphilis from an unknown source. Hutchinson, with the very keen observation of a very keen observer writes: "I have known enough of what is possible in reference to the acquisition of



syphilis, in all ranks of life, and under apparently the most unlikely circumstances, to induce me to disregard almost absolutely the denials of patients and to allow my opinion to rest not upon what I am told, but upon what seems probably true."

And "what seems most probably true" here is that the father acquired syphilis previous to his marriage and that he does not know or will not confess it, and that the mother who apparently remained free of symptoms, was pregnant three times with two miscarriages and one living tainted child.

AFFECTIONS OF THE ENDOCRINE GLANDS IN ACQUIRED SYPHILIS

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IT is a pleasure to state that in the preparation of this chapter, unquestionably one of the most difficult in the book, I have been greatly aided by the advice of Dr. Edward Hiram Reede, of Washington, who for a number of years has made a special study of diseases of the ductless glands. The literature upon the syphilitic affections of these glands is in an extremely unsatisfactory state, because almost no mention is made of the symptoms that accompany luetic affections of these organs, and yet this is not surprising, for the field is comparatively new, very few men are acquainted with the symptomatology of endocrine gland disorders, and the literature has never been properly collected. Hence, at the present time, syphilis of these glands is an almost unknown disease, at least so far as any really valuable data exists. It can safely be prophesied that the importance of luetic infections will increase as our knowledge spreads. We are now beginning to recognize that definite syndromes may be due to oversecretion, undersecretion and dysfunction of the ductless glands. Just how far syphilis is responsible for these secretory abnormalities it is still impossible to say, for in reading the case reports of ductless gland disease one but rarely finds any mention of a search for syphilis.

Barker groups the ductless glands as follows: (1) the thyroid gland, (2) the hypophysis cerebri or pituitary body, (3) the chromaffin tissues including the medulla of the suprarenals, (4) the cortex of the suprarenals, (5) the parathyroid glands, (6) the testes and ovaries, (7) the pineal gland, (8) the thymus, and (9) certain portions of the pancreas namely, the Islands of Langerhans.

As the work upon vegetative neurology increases, it becomes evident that the activities of the ductless glands are closely associated with the action of the vagus and the sympathetic nerves: it is probable that in the future it will be found that endocrinology will be recognized as but a branch of vegetative neurology.

Bibliographies concerning the general subject of endocrine gland disease and functions may be found in the works of Barker,[1] Biedl,[2] Falta[3] and Schäfer.[4]

SYPHILIS OF THE THYROID GLAND

The thyroid gland is supposed to have the following functions: it controls iodine metabolism; it controls the intracellular protein metabolism, its action being general, and its oversecretion emphasizing normal activity of all tissues; it is closely allied with the vegetative nervous system; the thyroid autocoid augments the effect of adrenalin simultaneously placed in the circulation, and may be found to augment the action of other autocoids.

There are two different types of hypersecretion, the sympathicotonic and the vagotonic. In the former there is well marked exophthalmos, marked tachycardia, dry skin, falling hair and alimentary glycosuria, while in the latter there is no exophthalmos, but a slight tachycardia and marked palpitation, sweats, hyperacidity of the stomach, diarrhea and unlessened carbohydrate tolerance. The two groups also show very different eye signs, for in the former, there is a negative von Graefe (dissociation between the movements of the upper lid and of the eyeball) positive Loewi (epinephrin mydriasis) and a positive Moebius (insufficiency of convergence) while in the latter the von Graefe is positive and the Moebius negative.

There is but little literature as to hyperthyroidism caused by syphilis but it undoubtedly can occur in early syphilis for we all know that infections may cause a temporary oversecretion. Levy-Franckel[5] reports eighteen cases of Graves' disease that developed late in the course of the secondaries. Thompson[6] states: "According to Gougerot three cases with symptoms of exophthalmic goiter which were improved by antisyphilitic treatment have been reported by Penzold." Poncet and Leriche[7] have recorded a case in a syphilitic woman who developed symptoms of hyperthyroidism and who was cured by arsphenamine. Clark[8] has also reported a case in a congenital syphilitic (see section on Congenital Syphilis). Finally Thompson[9] has very recently reported still another case in a man of seventy-two, who showed a pulse rate of 140, and protrusion of the eyeballs, as well as a definite gumma of the thyroid. Under antisyphilitic treatment all of these manifestations cleared up. I have seen one case of vagotonic hyperthyroidism in a woman suffering from cerebrospinal syphilis, which entirely disappeared under antisyphilitic treatment. In another instance a young negro girl came to the dispensary because of secondary syphilis. After she had been under treatment for some time (she received no iodides) she developed a large general swelling of the thyroid, and some signs of vagotonic hyperthyroidism. She was referred to Dr. Reede, who told me that she had previously had a mild Graves' disease. One would naturally think that gummous formation where there is a destruction of tissue would cause undersecretion, but this was not the case in either Clark's or Thompson's patient. It would seem that perhaps syphilitic changes in one portion of the gland may stimulate the remainder to oversecretion.

In conditions of hypothyroidism the gland can usually not be felt, the skin is thickened and dry, there may be supraclavicular fat pads, the face lacks expression, all of the metabolic processes are slowed the temperature is frequently subnormal, constipation is the rule, and there is evident lack of memory and slowness of thought.

There is very little literature as to the part that syphilis can play in causing hypothyroidism, however, one can not help feeling that if an interstitial thyroiditis exists, as occurs in practically all other organs, there should be some symptoms. As bearing upon this point Kohler[9] has reported a case where a woman of forty-eight had a tumor of the thyroid that disappeared under iodide: a concomitant myxedema also disappeared. Pospelow[10] has also reported an instance where myxedema developing in an undoubted syphilitic was cured by antisyphilitic medication. More observations upon this point are much needed.

However, the literature does deal with three distinct types of lesions, the diffuse swelling of the gland associated with early syphilis, gumma formation, and disturbances caused by the administration of iodine.

Engel-Reimers[11] has reported observations upon 250 cases of syphilis. Of 152 females, 86 showed enlarged thyroids early in the course of the disease, while 44 out of 98 males were similarly affected. However, the presence of preexisting thyroid enlargement was not rigorously excluded, neither was any mention made as to type of treatment employed, that is, as to whether the iodides were administered. "The swelling appears in the secondary incubation period or concomitantly with the first constitutional symptoms. It does not appear to be influenced by antisyphilitic treatment, but, like the swelling of the lymph glands, disappears gradually in the course of a year or two.'' Engel-Reimers described the enlargement as being confined to the lateral lobes, and as being soft and painless. Mauriac,[12] Lockwood,[13] Julien and others have described this condition. I am convinced that it is not common, for I have encountered but three cases in a large series where it was carefully searched for. In one of these cases later search revealed the fact that there had been a goiter of long standing that suddenly became much enlarged after the appearance of the secondary lesions, although no iodides had been employed. Davis [14] mentions the fact that the swelling may be hard and painful.

A number of cases of gumma of the thyroid have been reported. Davis[14] has collected all of the cases up to 1910, in addition to reporting one of his own, and more recently Thompson[6] has again reviewed the literature. The other case reports were by Wagner,[15] Ziegler,[16] Fraenkel,[17]. Mendel,[18] Thursfield,[19] Clarke,[20] Lancereaux,[21] Power,[22] and Poncet and Leriche.[7] The tumor is usually painless, may be either large or small, may or may not ulcerate, and may cause any of the usual pressure symptoms. The histology of the condition is identical with that of gummata in general. On the whole antisyphilitic treatment has been successful.

In 1906 Mendel suggested that some of the so-called cases of thyroid syphilis might be merely examples of iodine thyroiditis. He felt that most of the early cases were of this nature. This view has escaped the general attention that it deserves, in spite of the fact that symptoms of hyperthyroidism may be caused by large doses of the iodides. Other articles dealing with syphilitic thyroiditis are those of Hülth,[23] Shiron,[24] Rosenbauer[25] and Zoeller,[26] who gives an admirable historical review.

SYPHILIS OF THE PARATHYROIDS

We are fairly well informed concerning the functions of the parathyroid glands, knowing that they control the calcium metabolism of the body, and that a lack of their secretion results in tetany, or in paroxysmal contractions of the muscles, paresthesias and trophic disturbances. Concerning the overfunction of these glands the literature is silent. I can find no references concerning syphilitic lesions of the parathyroids, and yet it is reasonable to infer that some of the above-mentioned phenomena might be due to luetic lesions.

SYPHILIS OF THE THYMUS

The functions of the thymus are as yet not perfectly understood, as Reede[27] has well pointed out. Normally the gland is supposed to involute soon after puberty, but this is by no means always the case. Our knowledge of underfunction of the gland is very incomplete as the experimental evidence is conflicting, and as the clinical evidence has never been carefully correlated. Overfunction is supposed to result in the so-called status thymicus. Certain it is that the gland has to do with the development of the body. The literature contains a number of references to congenital syphilis of the thymus, but there are no cases of acquired lues of this gland upon record.

SYPHILIS OF THE PINEAL GLAND

Irritative lesions of the pineal body delay puberty, while destructive lesions cause precocious puberty. Tumors of the gland produce symptoms of increased intercranial pressure, certain focal manifestations, and some signs of disturbed internal secretions, chiefly premature puberty and changes in the carbohydrate tolerance. Concerning syphilis of the gland we are totally ignorant.

SYPHILIS OF THE PANCREAS

This subject has already been discussed.

SYPHILIS OF THE TESTES AND OVARIES

This subject has likewise been discussed.

SYPHILIS OF THE SUPRARENALS

Irritative lesions of the medulla of the adrenals, causing oversecretion, result in rapid pulse, increase in the blood sugar, increased blood pressure, shortened coagulation time, and irritability of the vasomotor system. Destructive lesions of the medulla naturally cause an opposite set of symptoms, namely, cyanosis, and sometimes heart failure. At this point it is interesting to note that it has been experimentally shown that arsenic and arsenic compounds may have a destructive action upon the medulla.[28]

Irritative lesions of the cortex produce the syndrome of suprarenal virilism, while destructive lesions produce Addison's disease, with its low blood pressure, weakness and pigmentation.

The low blood pressure, usually believed to be one of the symptoms of Addison's disease, is now believed by some of our best observers to be entirely due to weakness, and not to a primary change in adrenal secretion. There have been autopsies upon a number of cases which showed the classical pathologic findings of Addison's disease and in which a low blood pressure had never been observed.

Pathologists now recognize that syphilis of the adrenals, in the form of areas of round-celled infiltration, is very frequently found in autopsies upon patients dying of syphilis. Warthin[29] is very emphatic upon this point.

But little is known of the effect of secondary syphilis upon the adrenals. Various men have attributed the asthenia sometimes seen at this stage of the infection to changes in the adrenals, and Giuranna[30] has described changes in the cells, a finding that Sézany[31] was unable to confirm in autopsies upon three cases. However in the late stages of syphilis a few cases of Addison's diseases have been reported, one by Thompson[32] and another by Schaffner and Howard.[33] Addison's disease due to syphilis is probably commoner than has been believed.

Further information may be found in the writings of Jacquet and Sézary,[34] and Ribadeau-Dumas and Patii.[35]

SYPHILIS OF THE PITUITARY

The pituitary body consists of three portions, the anterior glandular part, a posterior nervous part, and an intermediate portion. Each has special functions. Irritative lesions of the anterior lobe stimulate the general growth of the body, a condition spoken of as acromegaly, and an abnormal development of sex growth and function. Destructive lesions inhibit growth and likewise sex growth and development.

Some of the late work would seem to show that the posterior pituitary body has no separate functions and that the changes which were attributed to disease of this portion of the gland must be assigned to dysfunction of the whole gland.

A considerable number of cases of gumma of the pituitary have been described, most of them in women, curiously enough. In many of the cases there was no clinical history, the patient having died soon after admission to the hospital, or the lesion having been found at autopsy. The symptoms to be expected would naturally be those of increased internal pressure, focal symptoms due to local pressure, and those due to lack of function.

In the cases reported by Stroebe[36] and Turner[37] the disease was very acute, death resulting in six weeks. Semicomatose attacks seem to be the outstanding feature. Other observers have reported polyuria, tremors, and amenorrhea. Cases have been reported by Sokoloff,[38] Birch-Hirschfeld,[39] Cushing,[40] Wagner,[41] Weigert,[42] Barbacchi,[43] Trosier,[44] Beadles,[45] Hektoen,[46] Rebandi,[47] Biabchi,[48] Hunter,[49] Woodley,[50] and Barker.[51]

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SECONDARY SYPHILITIC PERIOSTITIS OF THE MANDIBLE

Report of a Case

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THE ordinary involvement of the bones in early syphilis is an all too common complication to merit a case report. The following case is, however, so far as could be determined by an earnest search of the literature, almost unique, in the fact that the periostitis, which brought the patient to the hospital, affected the lower jaw alone. Fournier, Lancereaux and Connil make no mention of mandibular periostitis, nor is it to be found in the writings of contemporary syphilographers. I have likewise been unable to find mention of the condition in modern surgical texts, and in other late contributions. This apparent rarity of localization, and its occurrence in a patient, whose age ordinarily precludes secondary manifestations, would seem to make the case worthy of passing mention.

The patient, Mr. F. L., age sixty-three, presented himself at the Dermatological Service of the University Hospital on December 16, 1918, complaining of a painful swelling of the jaw and a penile lesion. The previous history is without interest, except that the patient denies all exposure during the past five years. The patient stated that the penile lesion appeared six months ago and was followed four months later by lesions on the inner surfaces of the lips and on the buccal mucosa. Four days before presenting himself the swelling appeared on the jaw, and up to the present had been quite painful.

Routine examination of the patient revealed a fairly well-nourished elderly male. The scalp was clean as was the skin of the face and likewise that of the trunk and extremities. Over the right mandible was an olive sized, rounded mass, definitely circumscribed, of firm consistency to the palpating finger and exquisitely sensitive to pressure. Objectively the mass was connected to the bone. The entire absence of redness, temperature and fluctuation at once eliminated the possibilities of the process being due to a pyogenic condition in the underlying structures. Likewise the picture was not that of a neoplasm. In short, the characteristics of the lesion gave the diagnosis *per se.* The x-ray plates were disappointing in that they did not reveal any marked changes, either in the periosteum or deeper portions of the bones, this being explained by the roentgenologist as due to the peculiar angle at which the exposure was made.

Further examination revealed an edematous prepuce and multiple discrete papuloerosive lesions over the shaft and scrotum. The mucous membranes were the seat of numerous, painful, papuloerosive lesions. There was an inguinal adenitis; the long bones were negative; the spleen and liver were not palpable; and the nervous system, including the pupillary reflexes, was objectively intact. The Wassermann reaction on the blood was four-plus positive. The patient was admitted to the service, placed on routine antisyphilitic treatment, and made a rapid and uneventful symptomatic recovery, the periostitis being one of the first lesions to disappear.

As has been stated above, involvement of the bones in early syphilis is an observation made far too frequently to merit special mention, yet the unique localization in this case, and its occurrence in a patient in the later decades of life has seemed deserving of more than passing notice. The latter interest in the case has been discussed in a recent paper from this clinic.

For the privilege of reporting this case and many courteous suggestions I am indebted to the kindness of my Chief, Professor Udo J. Wile.

SYPHILIS OF THE EYE—ACQUIRED FORM

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EYELIDS

SYPHILIS in any stage, from the primary sore to late gumma, may be met with in the eyelids. The frequency with which chancre occurs varies greatly according to different authors, but it would seem, in searching the literature, to occupy the third place after the lips and fingers. The location is usually at the intermarginal space. The mode of transmission varies greatly; for we find in some cases kisses as the cause; in others the use of infected linen; in Russia the pernicious habit practiced amongst certain classes of licking the eyes; at times autoinfection.

Practically all authors agree that the most common form of primary sore at the beginning has much the same appearance as a chalazion or hordeolum. It is essentially indolent and developmental changes are slow, so much so that diagnosis is rendered rather difficult until eventually the characteristic indurated ulcer appears. However it should be possible to subject serum from the ulcer to an examination under the dark-field thereby demonstrating the treponemata before the characteristic signs appear. As a rule, within two or three weeks after the initial lesion the lymphatic glands in the vicinity become involved, giving the evidence of commencing general infection, the submaxillary gland being involved, if the chancre is situated near the inner canthus, if near the outer canthus the preauricular gland, in accordance with the distribution of the lymphatic vessels of the lids.

The various syphilodermata are rare, though at times any one of them may occur, the usual site being at the folds and corner of the upper lid. Gummata are not uncommon, appearing in the late stage, generally located on the lid margin and, if superficial, breaking down to form characteristic ulcers. The necrotic process may be so extreme as to cause partial destruction of the lids. According to Hutchinson, Jr., gummata of the lids are found in women more frequently than in men, and the upper lid more often than the lower.

THE TARSUS

The tarsus is liable to syphilitic infection in the late stages, either in the form of circumscribed nodes, or a diffuse gummous infiltration, in which condition the lids become so thick that it is impossible to evert them. This condition shows little tendency to break down. If incised it shows no tendency to bleed and presents a lardaceous condition. The disease runs a long chronic course.

CONJUNCTIVA

Primary lesions occur rarely, the relatively most frequent seat being the conjunctiva of the lower lid and transition fold. The lesion presents a lardaceous swelling of the conjunctiva, with slight irritation and edema associated with profuse mucopurulent secretion.

A few cases have been reported of chancre of the bulbar conjunctiva, in which the lesion closely resembled, at first, a phlyctena. In the late stages papules, either single or multiple have been described. They show small tendency to break down and disappear under antisyphilitic treatment. As a rule gummata create more or less irritation as they involve the underlying structures. De Schweinitz calls attention to a particular type of conjunctival inflammation occurring in subjects of pronounced syphilis (conjunctivitis syphilitica) in the form of granulation similar to trachoma follicles. This condition does not respond to local treatment, but does to antisyphilitic treatment.

SCLERA

Gummata of the sclera, per se, are of such rarity that most of the text books devote little attention to a description of them. I have seen one case in a colored male, age about forty years, the gumma appearing as an almond-shaped tumor, projecting from the sclera midway between the limbus and equator. The color was of a dark cherry red, a zone of scleritis extending around the tumor, the scleral and conjunctival vessels greatly engorged and congested and the entire conjunctiva more or less edematous. The tumor was immovable and slightly sensitive to touch, lacrimation was profuse. The ciliary body, cornea, and iris were clinically not involved. The ophthalmoscopic examination was negative; Wassermann reaction, triple plus. Heavy doses of potassium iodide and inunctions of mercury caused the tumor to gradually disappear, leaving a faint trace in the thinning of the sclera.

The gumma may spread to the ciliary body, producing a cyclitis and if situated near the cornea it may also become involved. If untreated, the gumma may ulcerate, causing perforation and loss of the eye.

LACRIMAL SYSTEM

With the literature at hand, it has been impossible to find any true syphilitic lesions of the lacrimal gland, although de Schweinitz and Duane both call attention to an induration or gummatous infiltration, and Weeks quotes a case of primary lesion recorded by Anagarsa.

NASAL DUCT

Stricture of the nasal duct may occur as a consequence of luetic periostitis of the lacrimal canal, or extension from the nasal cavity. This causes an obstruction to the flow of fluid through the duct. The lacrimal sac soon becomes distended and the retained secretions become septic. By exerting pressure over the sac, pus can be pushed through the puncta into the conjunctival sac where it becomes a never ending source of danger, for the slightest corneal abrasion may thereby become infected leading to destruction of the eye.

CORNEA

Acquired syphilis seldom attacks the cornea; however, certain pathologic changes do occur, whose etiologic factor can be traced to the acquired form. Keratitis punctate syphilitica described by de Schweinitz, Mauthner, Fuchs and Hock appears in the later stages of the disease, and is characterized by the presence of minute circumscribed grayish white spots in the parenchyma of the cornea, usually confined to the center. These spots generally disappear without leaving any trace. The condition is unaccompanied as a rule by iritis or any circumcorneal injection.

DEEP VASCULAR KERATITIS

Deep vascular keratitis though occurring in both forms of lues, is probably met with more frequently in the acquired form. It appears as a pale red patch occupying a small portion of the circumference of the cornea, rarely over one quarter and seldom covering the pupillary area. Examination under the corneal loupe, discloses minute blood vessels, beginning at the corneal margin and extending into the deep layers of the substantia propria, which is more or less cloudy for a distance around the vessels. It is accompanied by symptoms of irritation, photophobia and disturbance of vision. The condition is of a more or less chronic duration, the cornea finally becoming transparent again. .(Weeks.)

NEUROPARALYTIC KERATITIS

Neuroparalytic keratitis is generally conceded to be due to atrophic disturbance of the trigeminus, consequently this condition can be at times traced to syphilitic deposits, along the course of the nerve. In this form of keratitis, a grayish infiltration of the cornea first takes place in the center which generally spreads until the entire cornea may become involved with the exception of a narrow margin around limbus, which usually remains free. Sloughing generally follows with the loss of the entire cornea. A striking fact is that the eye shows practically no irritation, ciliary injection is present, there is no lacrimation and the patient does not complain of pain. When tested the cornea is found to be insensitive.

Gumma of the cornea has been reported, but is exceedingly rare. In a case reported by Terson, there was a grayish yellow localized infiltration of the cornea accompanied by violent iritis. Luetic treatment was given with the result that the infiltration disappeared leaving a dense scar.

LENS

It is extremely doubtful whether syphilis ever directly affects this structure, it being of epiblastic origin. Following any inflammation of the ciliary body, the nutrition of the lens is liable to be interfered with, in which case it is apt to become opaque. For this reason, individuals affected with syphilis are more prone to cataract than those unaffected with the disease.

The eyes affected with cataract should be examined carefully for any sign of lues, for these cases are apt to be complicated with choroiditis, in which case the prognosis as to restoration of useful working vision should be guarded.

UVEAL TRACT

Bearing in mind the anatomic, physiologic and pathologic continuity of the different portions of the uveal tract, it seems scarcely conceivable that an inflammatory condition can be strictly limited to a single part; nor is this so; but for convenience sake we speak of that particular part as being inflamed, when certain specific signs and symptoms present themselves which clinically point to that part as the one most involved. Being of mesoblastic origin and taking into consideration the well-known fact that syphilis exhibits a peculiar affinity for attacking connective tissue elements, it is small wonder that syphilis enters so largely as an etiologic factor in all inflammatory processes of this particular structure of the eye.

IRIS

As early as five or six weeks after the initial lesion, the roseola syphilitica has been observed in the iris, and in some cases even before the appearance of the cutaneous eruption (Roemer). Clinically localized hyperemias are seen in the center of the iris, which portion is abundantly supplied with minute vessels, and are supposed to be due to capillary emboli of treponemata. How often this condition occurs is difficult to ascertain, owing to the fact that it causes no trouble in the iris and quickly disappears.

Almost any grave disease may cause inflammation of the iris, but according to different authorities, syphilis has been found to be the etiologic factor in from 40 to 70 per cent of all cases, whereas the percentage of cases of syphilis which acquire iritis during the course of the disease varies from .42 to 5.37 per cent (de Schweinitz). Hence, it is seen how vitally important it becomes to ascertain at the earliest possible moment the etiology of any case of iritis, especially so as all ophthalmologists admit that frequently it is impossible to differentiate syphilitic iritis from iritis arising from other causes.

Iritis in all its forms, from whatsoever cause, presents certain conditions in common; viz., pericorneal injection, due to injection of the anterior ciliary vessels producing the characteristic deep pink color.

In conjunction with this the conjunctival vessels are always engorged; turbidity of the aqueous due to exudate, blood or pus. Change of color in the iris is pronounced, due to the congestion and swelling whereby the iris pattern is obliterated, producing the well known "muddy iris." The pupil is contracted, due in part, to hyperemia and in part to irritation of the peripheral nerve filaments. Formation of posterior synechia or attachments between the anterior capsule of the lens, and the iris vary in size, number and firmness. The iris may be bound down throughout the entire pupillary margin by the inflammatory process. These inflammatory bands are easily demonstrable by the installation of atropine, giving the characteristic irregular pupil of iritis. The pain is severe, throbbing in character, not confined to the eye itself, but extending to the temple and down the side of the nose and at times extends even to the teeth. The vision is disturbed in proportion to the amount of cloudiness which occurs in the media.

In cases of iritis where there is involvement of the ciliary body, the cornea under oblique illumination is found to be hazy and upon close examination, deposits are seen on Descemet's membrane scattered over a triangular area of the lower portion of the cornea. These deposits are leucocytes, which are deposited by the aqueous humor upon the back of the cornea and remain there. They may contain pigment granules, showing their origin from the uveal tract (Parsons).

It is stated by Friedenwald that in all cases of iritis, the cornea is affected either with infiltrations into the substantia propria or with deposits on Descemet's membrane. The former are occasionally in evidence, the latter always.

Roemer divides all forms of iritis into two large groups: those in which the anterior surface of the iris is the part particularly affected, and those in which the deeper layers are affected. He likewise groups the etiologic factors into those which produce inflammation of the deeper layers, viz., syphilis and tuberculosis. However, the differentiation can not be made save with the aid of a Zeiss loupe and even then the two conditions undoubtedly blend to such an extent that this, as a diagnostic point, can not be relied upon. Hence, in cases where the physical examination and history do not conclusively point to the cause, it is necessary to resort to the serum diagnosis. In fact all cases, in my opinion, should be subjected to this most valuable test.

Syphilitic iritis usually makes its appearance in the form of plastic iritis in the early stages of the general affection, usually between the second and ninth month, although it may be delayed until the second year. Both eyes are usually affected, though not always simultaneously. It is generally acute, and after a cure does not have the tendency to recur as the iritis following rheumatism or gonorrhea.

IRITIS PAPULOSA OR TRUE SYPHILITIC IRITIS

In the form of syphilitic iritis described in the preceding paragraphs etiologic diagnosis could be made only after a thorough physical and biological examination of the patient. This is not the case in iritis papulosa; here the eye presents certain well-defined clinical signs which immediately suggest lues to the examiner.

There is a high degree of injection of both conjuctival and ciliary vessels. The iris is discolored and its pattern obscured to a moderate degree. Examination with oblique illumination reveals the pressure of nodules situated usually at the pupillary border of the iris, although they are occasionally seen near the ciliary border or even in the tissue between. They present a yellowish red or brown color and are about the size of the head of a pin. These nodules project into the anterior chamber or pupillary space. Focal illumination also brings out posterior synechia.

Microscopic studies bring out the fact that there is no sharp line of demarcation between specific plastic iritis and iritis papulosa, as it has been demonstrated microscopically that there are nodules present in all cases of plastic iritis which clinically give no sign, being too minute to be observed.

GUMMA

This condition occurs in the late stages of the disease and is of greater rarity than the papule. It is usually a solitary tumor of considerable size and appears almost always at the ciliary margin of the iris; is usually seen in only one eye. The iris is more or less involved as is the ciliary body. It may undergo degeneration or may proliferate and fill the anterior chamber or it may perforate the sclera by extension through the ciliary body.

Examination of the cornea in the vicinity of the tumor will generally show a slight haziness and the formation of deposits in Descemet's membrane. In case of recovery a scar is left in the shape of atrophy of the iris fibers at the site of the tumor.

CILIARY BODY

Inflammations restricted to the ciliary body alone are exceedingly uncommon, owing to the intimate anatomic relationship between this structure and the rest of the uveal tract. Syphilitic cyclitis is essentially an iridocyclitis of the plastic type. The disease is acute, both eyes being affected, though not always simultaneously.

The symptoms leading to a diagnosis are the following; circumcorneal injection, neuralgic pains radiating from the eye through the head, extreme tenderness upon pressure over ciliary region; turbidity of the aqueous, posterior synechia binding the iris to the anterior capsule of the lens; a deepening of the anterior chamber; exudate or blood in the anterior chamber; opacities in the anterior layers of the vitreous; and deposits of exudation on the posterior layer of the cornea.

The tension is high or low according to the character of the inflammation. In severe cases the choroid, retina and optic nerve may be involved.

Gumma is of rare occurrence. It is usually monocular, is of relatively rapid development, and the iris is more or less involved. The condition is accompanied by neuralgic pain. Brixa reports a gumma accompanied with extensive syphilitic changes in other parts of the eye.

CHOROID

Next to iritis choroiditis is the most common luetic manifestation of the eye. The disease assumes the exudative form, and, whereas it is generally disseminated in character, yet it may be diffuse, circumscribed or central, hence it is not safe to attempt to make a diagnosis of syphilis by the appearance of any one particular form of choroiditis.

It occurs usually in the early stages of the disease, anywhere from the fourth month to the second year, although it may not appear until later. Both eyes are usually affected, and the disease runs a chronic course, lasting over a period of six weeks to three months or more. If seen in the early stages, the ophthalmoscope reveals the recent foci of inflammation as well-defined yellowish or grayish spots scattered throughout the fundus; occasionally retinal vessels can be seen to pass over them. These spots are due to infiltration of the choroid. The overlying retina is slightly cloudy and edematous. Small diffuse opacities are seen in the vitreous, usually in the posterior portion, owing to the exudate having passed through the retina. In the later stages the exudate in the choroid becomes organized, forming fibrous tissue which more or less destroys the normal structure of the choroid and overlying retina, so that the color of the spots gradually changes to white, due to the atrophy of the choroid and retina, whereby the sclera is seen to shine through. In the last stages, masses of pigment are seen heaped around the edges of the atrophic areas.

The symptom which first attracts the patient's attention is the diminution of vision. If peripheral, vision is very little affected, while if the macula is involved, there is a great diminution. There is a distortion of objects (metamorphopsia), straight lines being bent in various directions, occasionally objects appear smaller than normal; (micropsia): or at times larger (macropsia). This is undoubtedly due to the displacement of the rods and cones as the exudate in the choroid raises up the retina slightly. The prognosis should be guarded owing to the fact that there may be an extension of the disease to the retina and optic nerve, or forward to the ciliary body and choroid.

RETINA

Syphilis may manifest itself in any one of the various forms of retinitis, but, as a rule, it is either circumscribed or diffuse. In the former it makes its appearance near the disc, in the shape of a cloudy swelling which radiates along the course of the vessels; vitreous opacities are present. The nerve head is cloudy, of a yellowish red color, the edges are indistinct, the arteries are practically normal, while the color of the veins is darker; there is exudation along the lines of the vessels (perivasculitis). In the latter form the entire retina is edematous and grayish in color, and throughout the retina, and especially near the macula, grayish spots are present.

In syphilitic retinitis, hemorrhages into the retina are rare, though they may occur. The disease generally occurs in from one to two years after the infection, one eye may be affected, but as a rule both eyes are usually involved, but not simultaneously. About 8 per cent of luetics develop retinitis (Alexander). Whereas iritis is rare in other forms of retinitis it is by no means uncommon in the specific varieties; and likewise iridocyclitis is apt to occur.

The subjective symptoms are defective central vision, marked in the late stages, decrease in visual acuity under weak illumination, distortion of objects (metamorphopsia), irregular and concentric contraction of the peripheral field, positive scotomas in the central field. Although the onset is sudden the disease invariably follows a chronic course.

The prognosis depends upon the early beginning of appropriate treatment, and even then the condition may lead to one of total atrophy of the nerve. Syphilitic retinitis often leads on into an extensive involvement of the choroid, to which condition, the term chorioretinitis is applied. A great many authors consider this as in reality beginning in the choroid due to the extensive changes which occur in that structure, and the comparatively slight involvement in the retina, while, on the other hand, other authors consider it as purely a retinal disturbance, usually in the outer layers.

The ophthalmoscopic signs are: dustlike opacities in the posterior portion of the vitreous, cloudiness of the retina around the disc, which is more or less hyperemic, perivasculitis of the retinæ and choroidal vessels, numerous isolated yellowish or white spots of exudation beneath the retinal vessels throughout the choroid which follow the same course as in disseminated choroiditis, ending in atrophy.

The subjective symptoms are: vision diminished, flashes of light, night blindness, metamorphopsia, scotomata and contraction of the visual field.

A rare and peculiar form of retinitis, which may occur in syphilis was first described by von Graefe, and is that form of retinitis known as central relapsing retinitis. It occurs in the late stages of the disease and is marked by a sudden diminution of central vision which may last for a few days, when the vision is practically restored only to be followed by a relapse. The prominent symptom is a central scotoma of which the patient complains.

The ophthalmoscope reveals a yellowish or grayish cloudiness in the macula, which may entirely disappear after the first few attacks, but as the disease progresses, the changes in the macula and the choroid become pronounced.

Retinitis pigmentosa and retinitis proliferans, at times, have as their etiologic factor, syphilis.

OPTIC NERVE

This structure may be affected throughout its entire course, or any part of it may be the seat of the inflammatory process. The intracranial portion, according to Uhthoff (quoted by Parsons) is affected most commonly, for here it may be attacked by gumma, or by extension of gummous infiltration from the meninges, for the neighborhood of the chiasm is a favorite spot for gummous meningitis.

With the statistics at hand, syphilis seems to stand forth as an etiologic factor. Here, as in inflammatory conditions, a differential diagnosis can not be absolutely made by the ophthalmoscopic picture, although several writers bring out the fact that in papillitis of syphilitic origin there is very characteristic thickening of the retinal vessel walls. White striæ, which are the result of the inflammatory process, accompany the vessels out into the retina.

PAPILLITIS

Papillitis, or inflammation of the intraocular portion of the nerve, manifests itself externally by no sign except that the pupils are dilated in proportion to the diminution or absolute loss of vision. The ophthalmoscope reveals the following picture: increased redness of the disc, the margin becoming indistinct owing to the swelling of the disc, which gradually shades off into the surrounding retina. The retinal vessels are altered; the arteries are smaller than normal, and may or may not be tortuous. The veins are dark, distended and tortuous, especially so when they dip down from the swollen papilla into the retina. Hemorrhages are of frequent occurrence, situated on the nerve head, or in the surrounding retina and generally of a fan shaped character. The vision may or may not be affected.

The peripheral fields of vision may be affected or else there may be irregular or concentric contraction. The blind spot becomes larger as the swelling of the disc increases.

CHOKED DISC

Although tumors of the brain are by far the most frequent cause of this condition, yet syphilis can not be disregarded. The disc is immensely swollen, protruding out into the vitreous like a mushroom, the color is of a glossy grayish red. The arteries are small, while the veins are immensely distended and tortuous, resembling a bunch of angle worms. Occasionally hemorrhages are seen in the disc. The surrounding retina appears normal. The swelling of the disc is primarily due to edema.

Gumma at the base of the brain may be the cause of the choked disc in either one or both eyes.

RETROBULBAR NEURITIS

Externally the eye shows no symptoms, save the dilation of the pupil, which is in proportion to the defect of vision. The patient complains of central scotoma, and usually there is pain upon movements of the eyeball. The ophthalmoscope first reveals nothing pathognomonic, but in the later stages there is hyperemia of the disc, the arteries appear small, while the veins are engorged. The condition is one of interstitial neuritis, which is apparently located in the intraorbital portion of the nerve.

ATROPHY OF THE OPTIC NERVE

Atrophy of the optic nerve may be primary or secondary. Any of the above-mentioned inflammations of the optic nerve may naturally have as their termination atrophy, consequent upon the changes produced in the nerve by the inflammation, as primary atrophy is a symptom produced by certain diseases of the nerve itself.

In from 40 to 50 per cent of cases of progressive primary atrophy, tabes is the etiological factor, hence it behooves us to investigate for other symptoms of this disease. The ophthalmoscopic signs are: a bluish white appearance of the papilla, the lamina cribrosa is visible, the margins of the disc are sharply defined. The excavation which is shallow extends to the margin of the disc. Both veins and nerves are smaller than normal. The patient complains of a gradual decrease in vision. The fields of vision for colors are first affected in the following relations: green, red, blue and white. As the peripheral fields contract the central vision fails until finally total loss of vision ensues.

OCULAR MUSCLES

Syphilis is by far the most frequent cause of paralysis of both the extraocular and intraocular muscles and, now that the etiology of tabes has been definitely established by Noguchi, it is safe to estimate that it is the etiologic factor in at least 75 per cent of all cases.

Irrespective of the cause, paralysis of the extraocular muscles presents certain characteristic symptoms which are practically present in all cases; viz., diplopia (double vision), owing to the images for both eyes from an object falling on dissimilar points of the two retinas, and therefore, projected to different parts of the field; vertigo, owing to diplopia and defective orientation; limited motion of the eyeball in the direction of the action of the affected muscle; tilting of the head in order to correct as far as possible the diplopia; false orientation, whereby the patient is not able to locate objects in their true place with the paralyzed eye.

The seat of the lesion producing ocular paralysis may be cortical, nuclear, fasicular basal or orbital.

Lesions of the cortex with the exception of ptosis (Duane), never cause paralysis of individual muscles, conjugate paralysis being the result of such lesions. Lesions on the floor of the fourth ventricle, produce, as a rule, paralysis of several muscles, and generally it is bilateral. Fasicular lesions, as a rule, cause oculomotor paralysis of the same side with paralysis of the extremities of the opposite side. Basilar lesions, as a rule, affect various nerves in succession as those supplying the ocular muscles, the facial, the olfactory, the trigeminus, the optic nerve, etc. In orbital lesions, the muscles and nerves are usually affected mechanically and are diagnosticated by symptoms indicative of affection within the orbit, such as pain produced by pressure on the eyeball, protrusion of eyeball, monocular optic neuritis, etc.

Paralysis of the intraocular muscles is of frequent occurrence in syphilis and, as a rule, it is unilateral although it may be bilateral.

ARGYLL ROBERTSON PUPIL

Argyll Robertson pupil, that condition in which we find that the pupil fails to contract to light, but does to convergence and accommodation, is quite frequent in tabes. Usually it is bilateral, but it may be unilateral.

With regard to the seat of the lesion, de Schweinitz says, "It has been placed in the fibers which pass through from the proximal end of the optic nerve to the oculomotor nuclei by some authors, and by others it is considered to be nuclear."

Ocular palsies may make their appearance in the early stages of the disease, cases having been reported as early as the fifth or sixth month, however, they are more frequent in the later stages, especially is this so of the intraocular muscles. Statistics show that the third nerve is the one most frequently involved in syphilis. It may be partially or completely affected. A complete paralysis is easily recognized. There is complete ptosis of the upper eyelid and the patient is unable to move the globe except outward and downward, this movement being due to the noninvolvement of the sixth and fourth nerve. The pupil is dilated, and does not react either to accommodation or light. Diplopia is present.

TREATMENT

All cases of syphilitic involvement of the eye should be under intensive general treatment in connection with whatsoever local treatment each particular inflammation demands. Only the local will be touched upon in the following paragraph.

Nasal Duct.—If stricture is suspected, the punctum should be dilated sufficiently to allow the entrance of the lacrimal syringe, and water should be forced into the nose. If this is not possible, the duct should be probed. If this can be done easily, in all probability no other treatment will be necessary. However, if bony obstruction protects the passage of the probe, it is far wiser to remove the sac than to subject the patient to the wearing of a style, permanently, which necessitates the splitting of the canaliculus and the opening of the occluded nasal canal.

Cornea.—In keratitis it is important to keep the iris well dilated to prevent synechia from forming. Atropia 1 per cent should be used every two hours, hot applications every two hours, and the eyes should be protected from light by the use of dark glasses. In the late stages of keratitis, dionin is of aid in clearing opacities.

Iris.—By far the most important drug for local treatment is atropine, 1 per cent of which combined with 1 per cent of cocaine should be instilled in the eye every two hours. This treatment should be continued until all ciliary congestion disappears. In order to alleviate as much as possible the dryness of the tract produced by atropine, it is well to compress the tear duct after instilling the drug. Pain is relieved by hot applications, preferably moist, applied with some soft material. Leeches should be applied to the temple thereby reducing the congestion and aiding the action of the atropia. In some cases dionin in weak solution is exceedingly grateful.

Iridocyclitis.—Naturally the same treatment used in iritis should be immediately instituted in case of iridocyclitis, attention being paid especially to the tension, which in inflammation of the ciliary body is liable to be increased. However the atropia should be used, as the quicker the iritic involvement is got under control, the quicker the tension becomes normal. In cases of excessively high tension, paracentesis of the anterior chamber can be done. It is seldom that the increase of tension in these eyes leaves any permanent damage.

Choroid.—All use of the eyes should be prohibited and the eyes should be protected from all bright light by use of dark glasses. The iris should be kept under inspection and proper treatment instituted in case of extension of the inflammatory process.

Retina and Optic Nerve.—Protection of the eyes from light and absolute rest from all use.

Intentionally, no mention was made of the use of arsphenamine in ocular affections in the previous paragraphs, as it was thought best to briefly outline some of the more recent opinions brought forward by various ophthalmologists.

When arsphenamine was first introduced to the medical profession, ophthalmologists, realizing that it was an arsenical preparation, were loath to begin the administration. In reported cases of syphilis of lids it has acted promptly. The best results so far, according to literature, seem to be found in inflammation of the uveal tract, especially in the cases of nodular iritis, several cases having been reported in which a definite cure was effected in a few days.

Choroidal lesions have also cleared up rapidly under its administration.

In cases of the involvement of the retina and the nerve, there is a great diversity of opinion regarding its use. Many cases are on record where optic neuritis and neuroretinitis have followed its use, especially when the case is complicated by retinal hemorrhages. Dolganoff, however. states that arsphenamine has no deleterious effect on the nervous elements of the eye, while various others claim that ocular inflammations following its use are to be looked upon as further evidence of lues and the treatment should be intensified, combined with mercury and potassium iodide.

In the ocular palsies, opinion is also divided, yet it appears from case reports that, if the treatment is begun early, satisfactory results are obtained.

Where most was expected of it, arsphenamine has singularly failed, namely, in interstitial keratitis. Many explanations have been brought forward, but, so far, none are satisfactory. In nearly all cases where it has been used, the second eye had become involved, hence, it does not seem to even have a prophylactic effect. Lamb advocates the subconjunctival injection of salvarsanized serum (Swift-Ellis method) and reports satisfactory results in many cases of iritis, chorioretinitis and involvement of the nerve.

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ALCOHOLIC ARGYLL ROBERTSON PUPILS?

Alcoholic Psychosis Simulating Neurosyphilis*

A Case Report

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THE cause of the Argyll Robertson pupil is not definitely known. Whatever the mechanism, however, it is so characteristic of neurosyphilis that its occurrence in nonsyphilitic psychoses is so rare as to be of unusual interest.

In the recent influenza epidemic several instances of fixed pupils with febrile delirium were observed here and have been reported by me elsewhere.[1] The work of Blin[2] will be recalled in which he claimed the presence of occasional Argyll Robertson pupils in cases of dementia precox.

An instance has recently come to our attention of the association of the Argyll Robertson pupil and other reflex changes commonly associated with neurosyphilis in a patient not suffering from neurosyphilis, or from influenza, or from dementia precox. The only demonstrated etiology was acute alcoholism. With the fixed pupils there was a speech defect, a paretic facial expression, tremulous tongue and hands, unequal knee and ankle jerks, and a rather defective memory. Altogether this made a fairly typical picture of "alcoholic pseudoparesis.[3] An outline of the case follows:

M. K., an Irish-American longshoreman of fifty, was sent from the City Hospital with a history that he had been "brought in by the police, fought viciously, and would not speak." The following morning he gave his name and age, but no further information, and was sent to the Psychopathic Hospital for further observation. There he gave his birthplace, his parentage, his occupation, and admitted excessive alcoholism. He was at this time somewhat irritable, but answered the necessary questions with the addition of a certain amount of wet humor.

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*A contribution from the Boston Psychopathic Hospital, Series of 1919.

A short time afterwards he was seen in the wards, gave his name as "B. Y. Sullivan," disclaimed knowledge as to the date or place, and said he had been here about six months. The following day he was still somewhat restless and showed gross judgment defect, such as expectorating upon the floor. At no time did he show any evidences of decreased sensorial receptivity.

A mental examination was made on the third day. He was accessible and fairly co-operative, rather dull, somewhat surly, but not discourteous. His orientation was precise in all spheres. His memory showed in addition to amnesia for recent events a more or less patchy defect and his calculating ability and retention of school knowledge were very poor. He admitted having had delirium tremens several times, but denied syphilis. Of the present attack he remembered only that he had left work to go on a vacation, had come to Boston, and had entered upon a long spree, and that he was arrested by the police. He recalls a vague delusion that he was playing some sort of game in the way of throwing pieces of paper on the floor. There were no persistent delusions or hallucinations. His insight was good; his attention somewhat wavering; associations rather slow; emotional tone fairly normal and motor status quite so.

A physical examination showed him to be a heavy jowled, powerfully built man with a smooth, ironed-out face, with a coarse tremor of the hands. Pupils were round, regular, the right slightly larger than the left; both were typical Argyll Robertson pupils, reacting to distance, but not at all to light. The arm reflexes were lively, but equal. The right knee jerk and ankle jerk were greater than the left. There were no other important physical findings except for some thickening of tibial periosteum and a blood pressure of 150-90. There was a distinct speech defect, particularly with the conventional test phrases.

With no more data than these, the diagnosis seems quite impossible. The history is distinctly that of an alcoholic psychosis; the physical findings are conspicuously those of neurosyphilis. The mental symptoms are compatible with either.

The spinal fluid showed no globulin, a normal quantity of albumin, one cell, and a negative gold sol reaction. The Wassermanns on both spinal fluid and blood serum were negative.

The man was discharged on the ninth day with a diagnosis of acute alcoholic psychosis, recovered.

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ROENTGENOLOGIC DIAGNOSIS OF SYPHILIS

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(Received for publication, March 19, 1919)

IN the proper treatment of any infectious disease, with a specific drug or serum, the earlier the treatment is instituted the greater is the prospect of cure. This is particularly true in the treatment of malaria by the use of quinine, and the proper treatment of syphilis is no exception to this fundamental principle. The fate of the syphilitic depends on this principle, for the prognosis is in direct proportion to the early inauguration of proper treatment.

It is incumbent on the physician to remember that a short interval may exist between an apparently innocent genital lesion and a latent state of paresis.

The anamnesis as regards syphilis is proverbially unreliable; however, the dark-field examination, Wassermann reaction, and clinical evidence, place such a triad of reliable data in our hands as to make it a culpable act whenever one fails to recognize this greatest of scourges.

The roentgen ray has placed itself in the scope of diagnosis of syphilitic manifestations. Its role is important in the occasional recognition of unsuspected syphilis.

Skeletal syphilis has long been recognized roentgenologically. Syphilis is one of the greatest bone producers, therefore, we naturally find marked periostitis. It produces two types of periostitis; first, the ordinary inflammatory type, laid down in striæ parallel to the bone, which is the commonest form; second, a serrated or tooth-like production which is the least common of the two, although this form is the most characteristic. Unfortunately this is rare, but when found it is typical of syphilis. No other form of periostitis manifests itself in this way. Syphilis is the one constitutional lesion which produces more bone than any other. It may manifest itself any time after three weeks.

Syphilis of children is usually congenital. Syphilis of adults is nearly always acquired. In children syphilitic arthritis produces fluid in the joint and thickening of the periarticular tissues. There are erosions at the side and edge of the epiphysis and on the diaphyseal side. It is accompanied by a certain amount of periostitis and is generally multiple in type. In adults we have marked swelling, thickening of the synovial membrane and fluid in the joint. This type does not go on to cartilaginous destruction; therefore, when the disease subsides we have a perfectly normal joint. Roentgenologically it is very similar to acute polyarticular rheumatism, fortunately the syphilitic infection produces a small area of periostitis at the point where the cartilage of the joint ceases and the periosteum of the bone begins. This periostitis associated with periarticular swelling and fluid in the joint is fairly characteristic of a syphilitic lesion.

The Charcot joint must not be confused with the acute syphilitic joint, since the changes in the former are neuropathic rather than infectious and are characterized by great destruction of the joint with splitting off of large fragments of bone, which lie free in a swollen joint filled with considerable fluid. In addition the ends of the bones are eburnated. The bones are not atrophied because of disuse, which would indicate that the joint was not kept at rest. Joints which undergo any degree of disorganization are nearly always painful and are kept at rest; consequently marked atrophy of bone is evidenced; therefore, when one sees a highly disorganized joint without much atrophy of bone one should consider the possibility of Charcot's joint rather than an infective arthritis.

Cranial syphilis is classified under chronic inflammation of the skull. The skull is a frequent site of luetic manifestations.

The regions most often affected are the frontal, temporal and parietal bones, occasionally the base. When the base is involved, it is found chiefly in the sphenoid bone.

The formation of syphilitic granulation tissue has its origin in the periosteum, in the dura, in the mucous membrane or in the bone marrow.

The skull may become affected in all stages of syphilis.

Even in the early stages of the disease flat swellings have been observed consisting of granulation tissue between the bone and periosteum on the outer surface of the bones. The underlying bone is osteoporotic, and the external table is perforated by many canals. The medullary spaces are widened. In the stage of healing one can

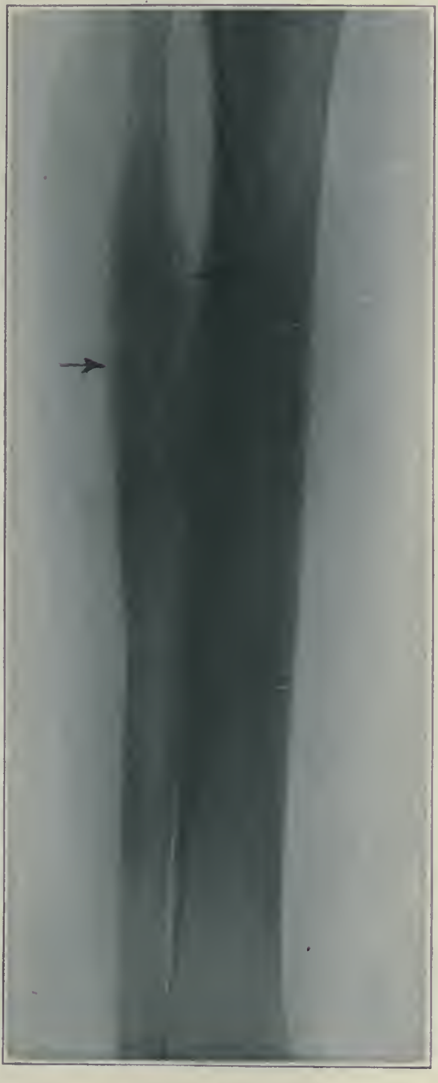

Fig. 1.—Syphilitic periostitis of fibula.

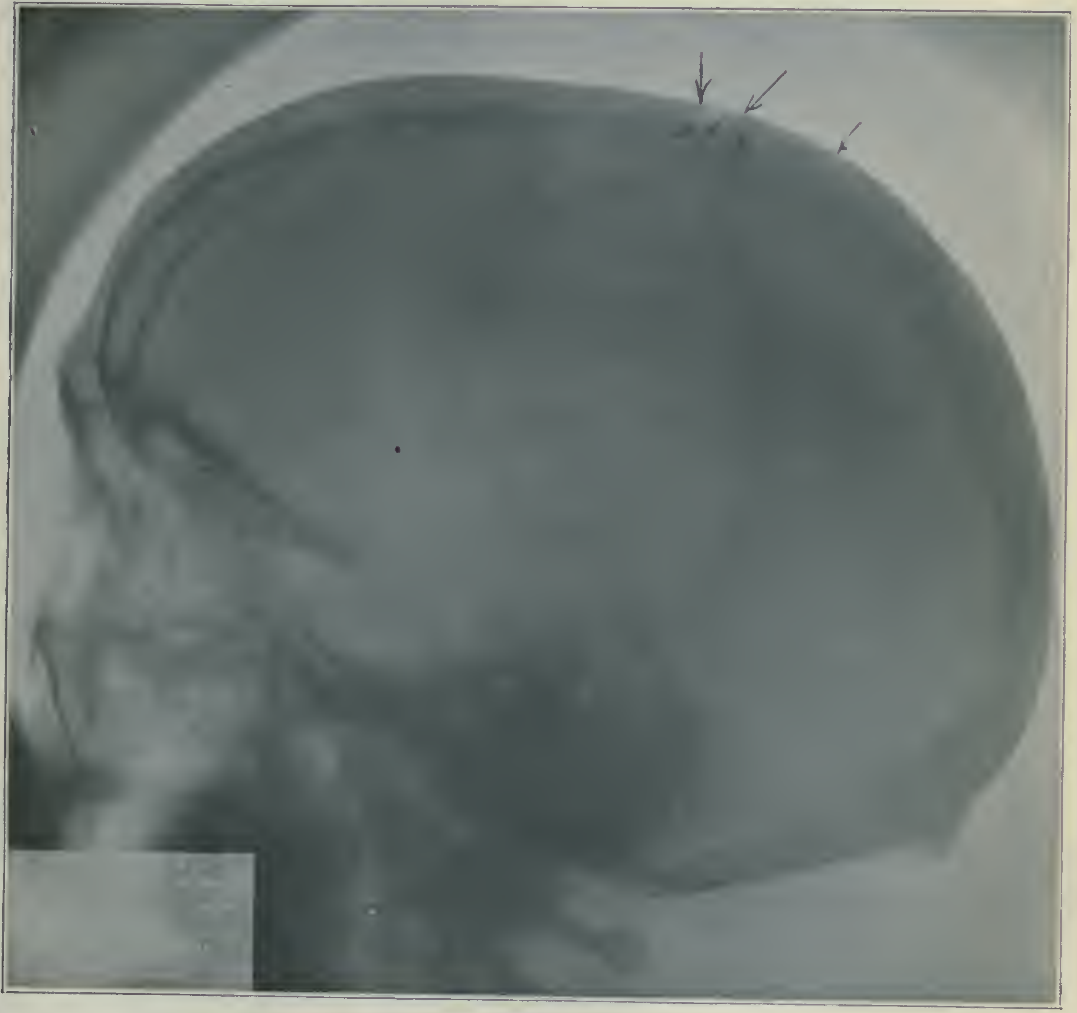

Fig. 2.—Syphilitic osteoporosis.

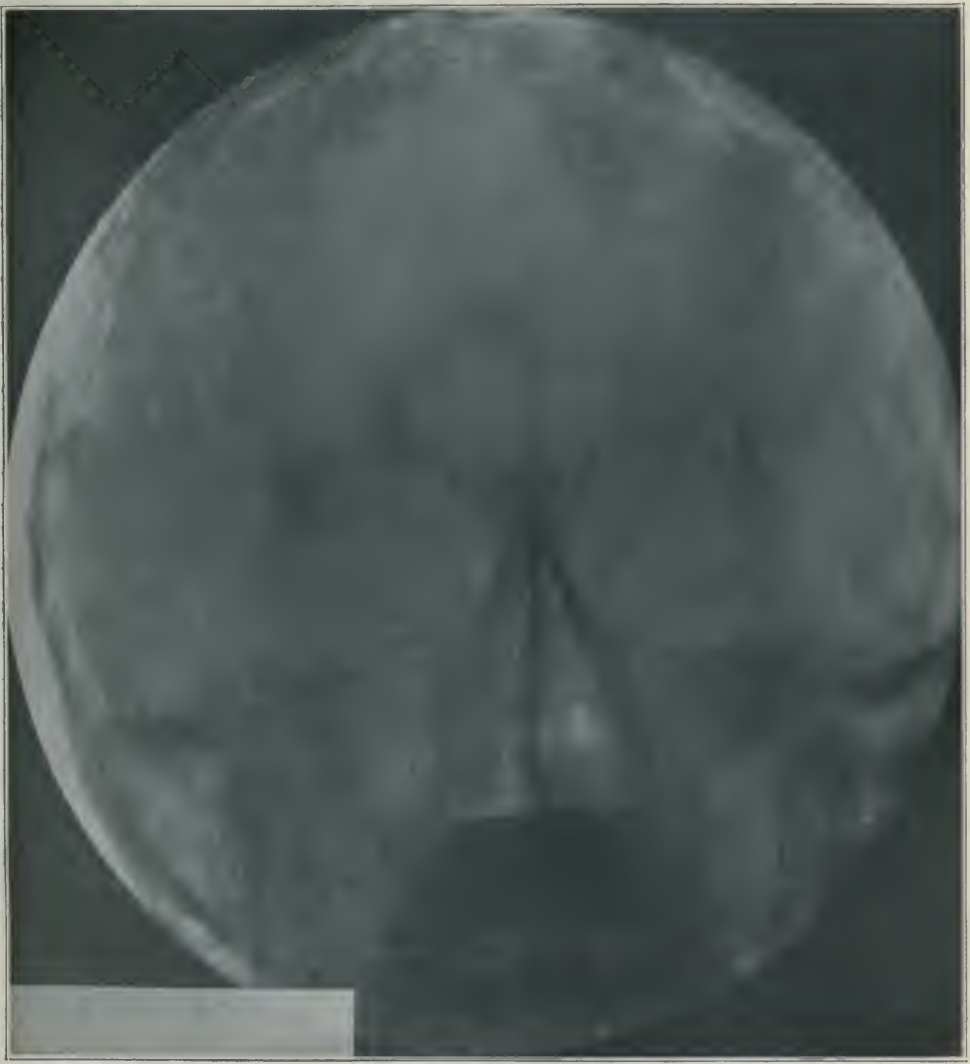

Fig. 3.—Syphilitic osteoporosis.

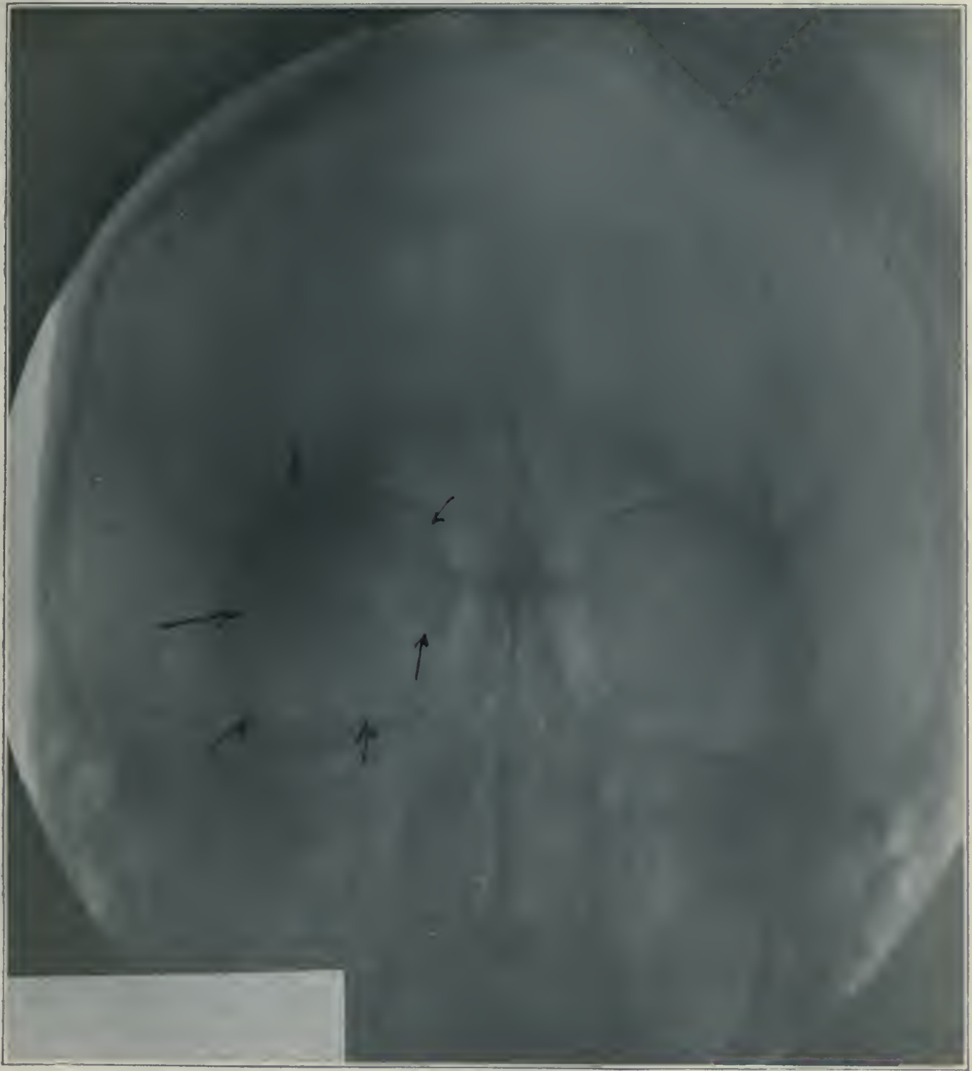

Fig. 4.—Periosteal production of right orbital walls with slight exophthalmus. Wassermann + + + +. Therapeutic results good.

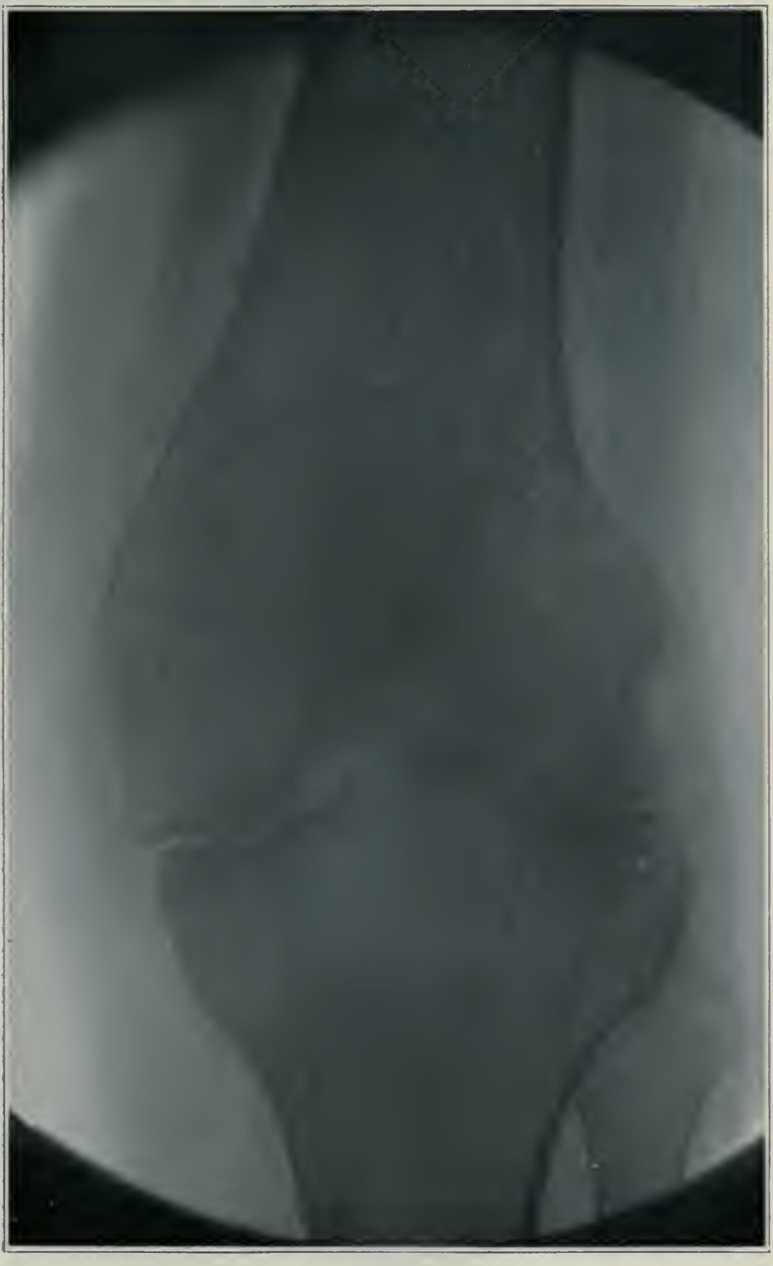

Fig. 5.—Charcot's joint.

see the prominence of the skull wall corresponding to the tophus and the increase in density of the bone structure.

Circumscribed gummata appear as defects with sharp, crescentic edges. The superficial ostitis appears as a mottling on the roentgenogram with slight areas in the bone shadow between islands of normal or sclerotic bone.

Hereditary syphilis manifests itself on the skull in three ways; first, by ulcerative processes, second, through disturbance of growth in the sutures and tissues, and third, through hydrocephalic enlargement. These types can be recognized by roentgen examination.

Visceral syphilis is gaining more prominence than heretofore, because of its prevalence and seriousness; the skin manifestations are quite subordinate in gravity of consequences.

The aorta is a frequent seat of syphilitic invasion, and unfortunately in searching the literature relative to this condition one is impressed with the paucity of information on that particular stage, namely, syphilitic aortitis. Great stress has been laid on the terminal lesion of aneurysm and aortic valvulitis.

The first anatomic studies of syphilis of the aorta were made by Morgagni in the middle of the seventeenth century. Later studies by Dohle and Marchand aroused considerable interest. They described the pathologic changes as mesaortitis and were impressed with coincident syphilitic lesions elsewhere. It remained for Benda, Richardson and Wright to establish proof of specificity by staining the spirochetes in the arterial wall successfully.

The interest surrounding the recognition of syphilitic aortitis today, occupies the same position as did tuberculosis, thirty years ago, attention being paid only to cases which are markedly advanced and far beyond remedial response. More attention must be paid to incipient aortitis, as the only hope of cure lies in its early diagnosis.

Dieulafoy classifies syphilitic aortitis into several types:

1. When the disease is confined to the first portion of the aorta.
2. Syphilis of the aortic valves with incompetence.
3. Aneurysmal forms.
4. Obliteration of the coronary vessels.

Types one and three are fruitful fields of applying the roentgen examination.

Often the symptoms are extremely vague, not severe enough to alarm the patient, but from the fact that chest symptoms are instantly associated with tuberculosis, the patient comes in for a chest examination.

The symptoms are: 1, Pain, usually substernal, with a sense of constriction, often radiating into the bronchial plexus with the characteristic arm localization. 2, Indefinite symptoms; such as fatigue, hoarseness, cough, fever, dyspnea and cyanosis. On roentgen examination a revelation of aortitis is perceived, virtually clinching the diagnosis.

The aorta should be examined fluoroscopically in all positions; particularly the left anterior oblique, which often reveals definitely, even a moderate enlargement of the first portion of the arch. One can see the enlargement to the left with obliteration of the aortic knob, also in the more advanced cases the enlargement is both to the right and left with increased density of the aortic shadow and a reduction of the aortic pulsation. This is a notable prognostic sign, also the existence of marked atony can be noted by asking the patient to cough vigorously and observing the undulating effect on the aorta at the time of release of the increased intrapulmonary pressure. Should a decrease of pulsation exist, marked sclerosis should be suspected; and if undue and pronounced expansile pulsation takes place, atony is present.

Plates should be taken, particularly teleroentgenographically.

The axiom of early recognition to obtain cure applies significantly in this malady.

Syphilis of the lung is now recognized as occurring more frequently than was formerly supposed. Laennec, Depaul and Virchow did painstaking work on this subject; it remained, however, an obscure entity until the discovery of the Spirocheta pallidum, Wassermann test, the introduction of salvarsan by Ehrlich and the extensive use of the roentgen rays in the interpretation of lung disorders.

Because of the frequency of pulmonary tuberculosis any pathologic change is liable to be ascribed to tuberculous infection.

Negative Wassermanns in syphilitics are by no means uncommon, and a positive Wassermann merely indicates that the patient has syphilis but not that the pulmonary condition is luetic. Roentgenographically, lues does not give a characteristic picture, for the peribronchial thickening is found in other pulmonary conditions; however, pulmonary tuberculosis does give a somewhat roentgenographic entity, thereby differentiating these two plagues. Should

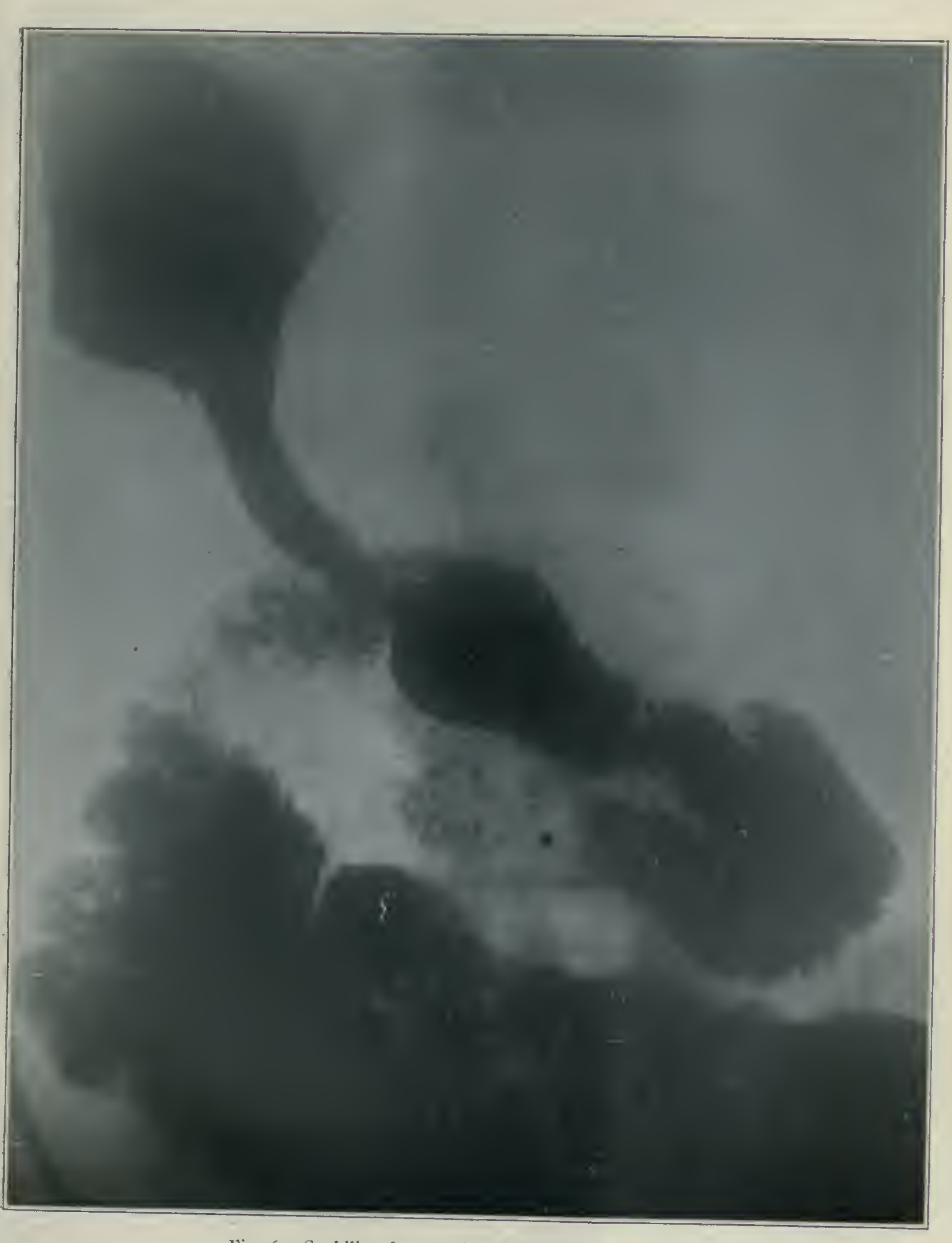

Fig. 6.—Syphilis of stomach. Wassermann + + + +.

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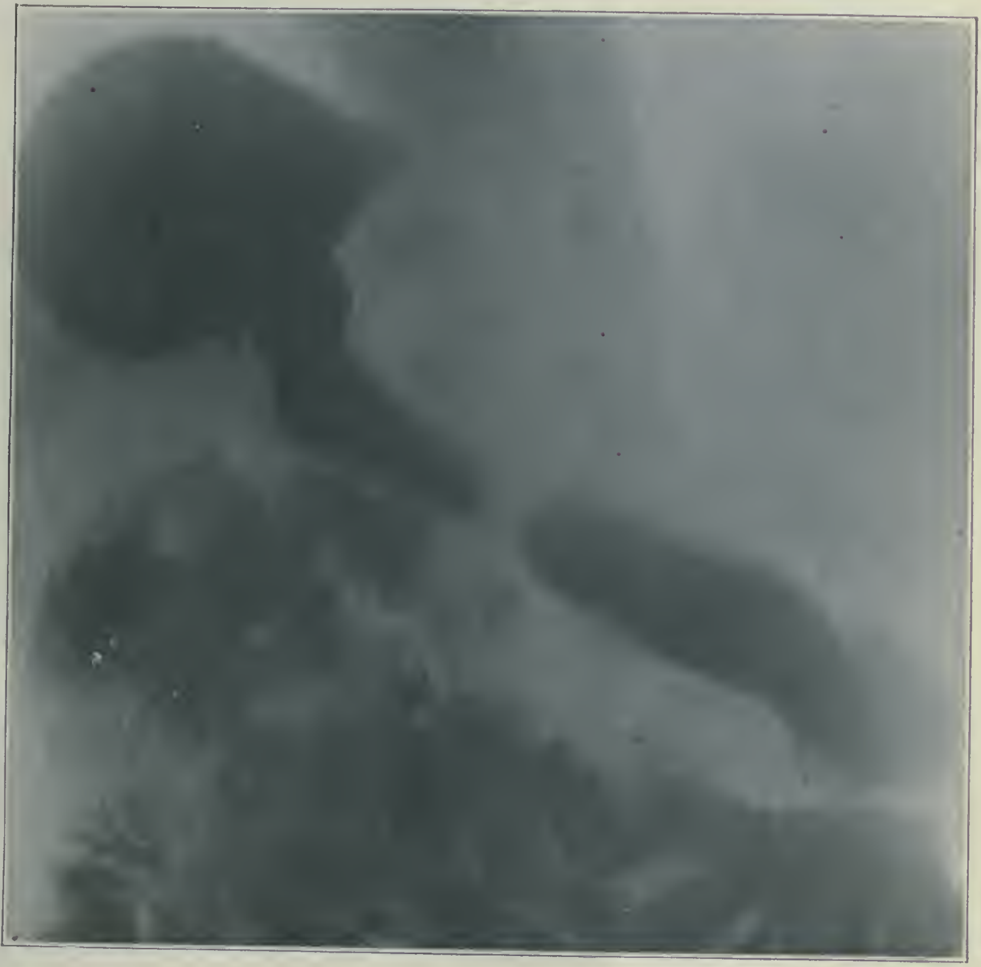

Fig. 7.—Same case as Fig. 6 after five months' treatment. Greater patency of corpus of stomach with increase in size of cardia and pylorus. Gain in weight of 28 pounds.

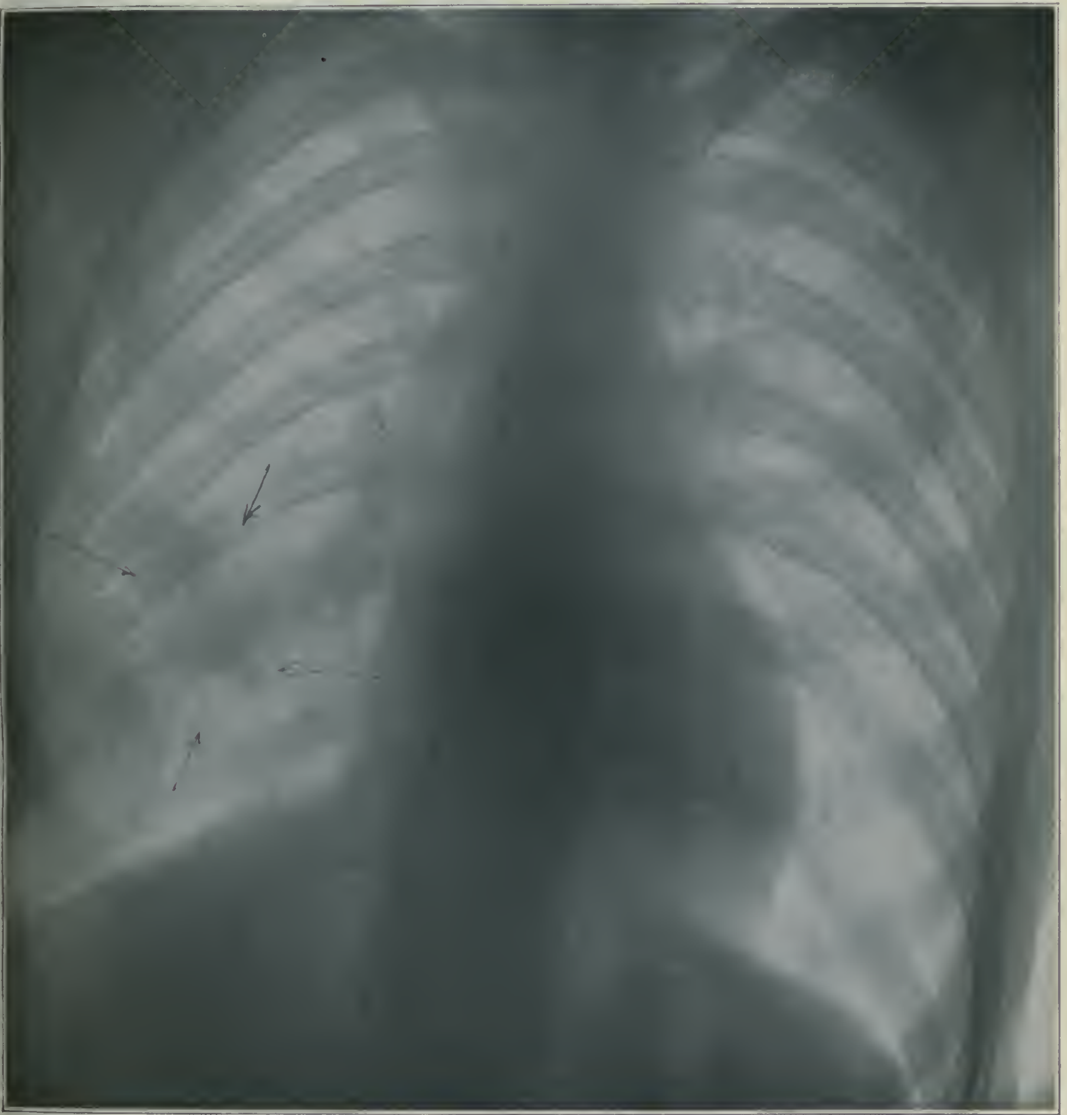

Fig. 8.—Pulmonary syphilis, same case as Figs. 6 and 7, slight dilatation of ascending aorta. Taken at time of gastrointestinal examination and before institution of treatment.

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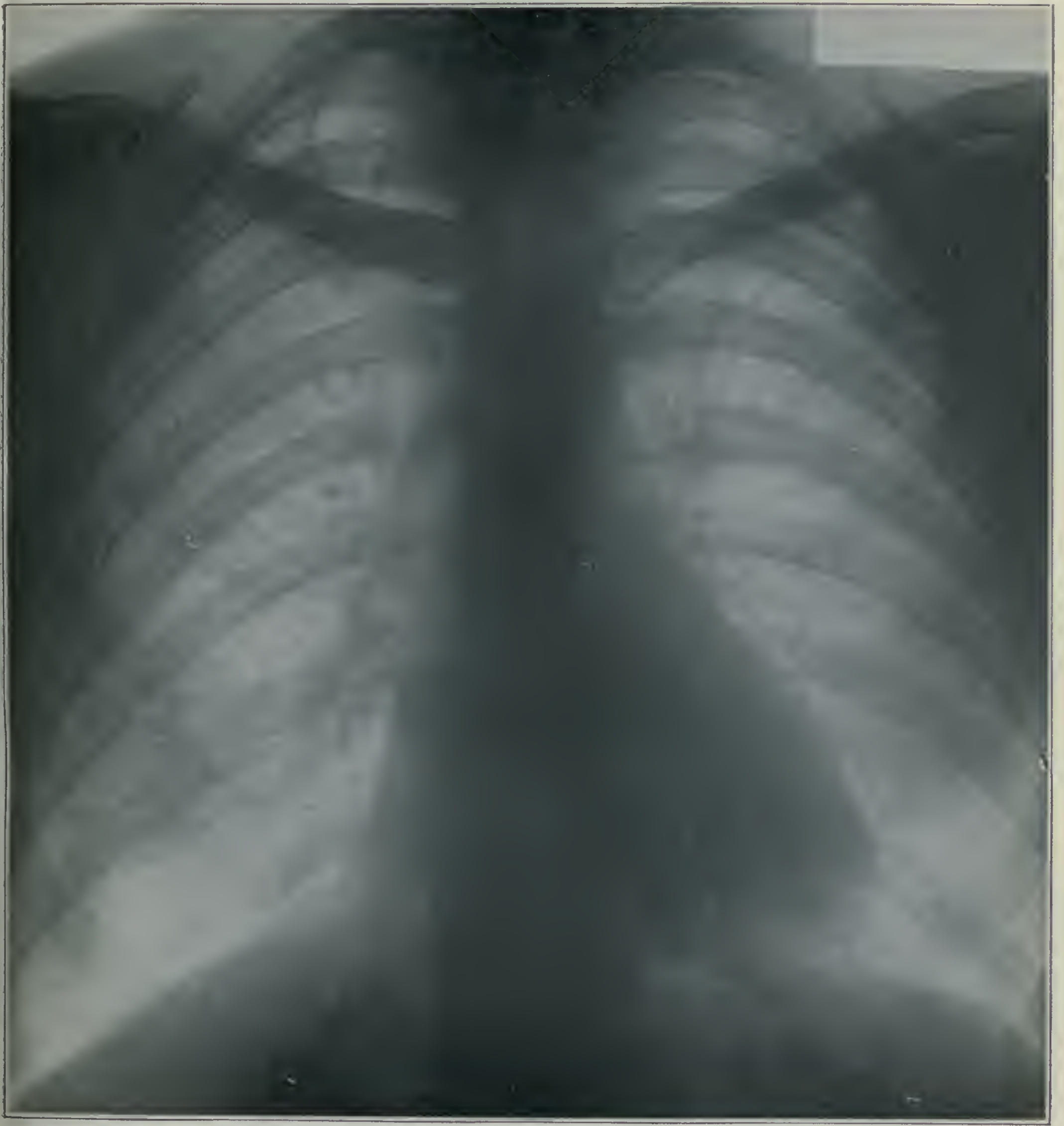

Fig. 9.—Same case as Figs. 6, 7, and 8. Complete obliteration of pulmonary lesion after five months' treatment.

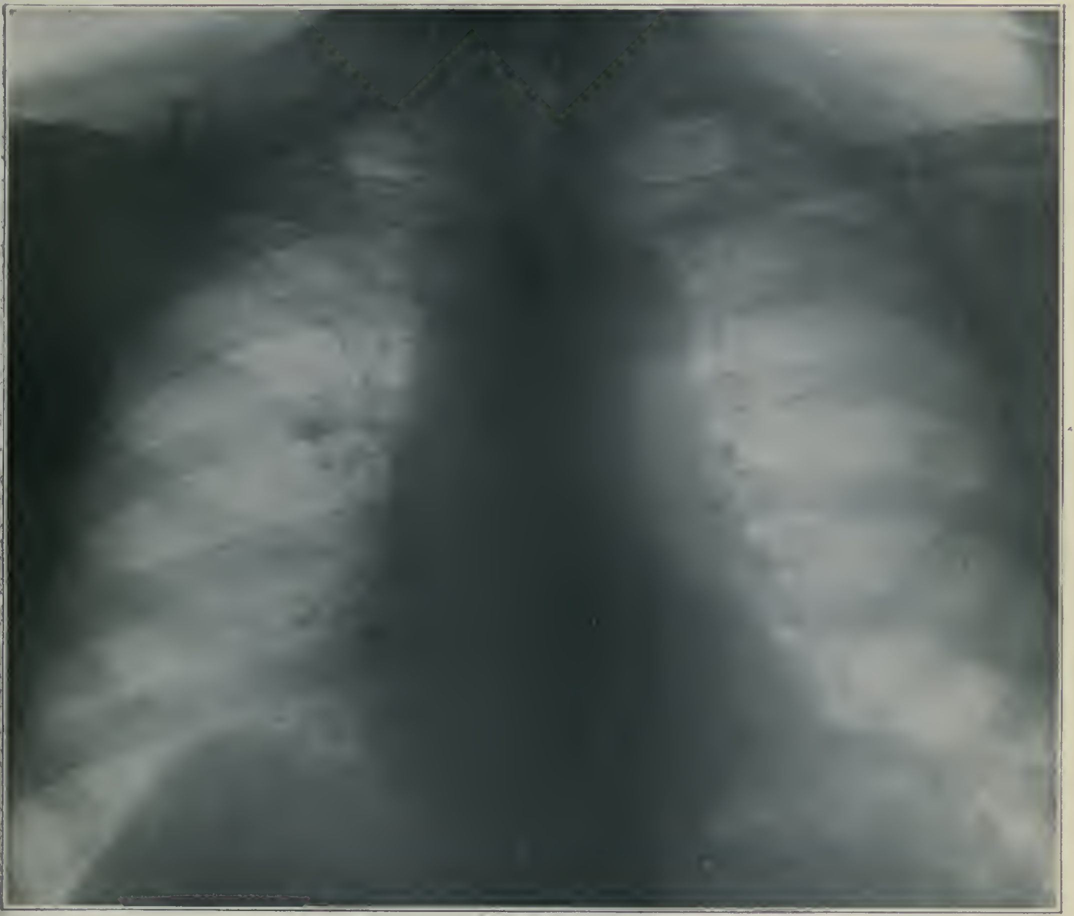

Fig. 10.—Syphilitic aortitis.

an associated dilated aorta coexist, the possibility of syphilitic infection is more pronounced.

Gummata produce striking shadows but must be differentiated from malignant growths.

In conclusion it is proper to state that even today our knowledge of pulmonary syphilis and our ability to diagnose it leaves much to be desired.

In concluding this paper mention of gastric syphilis must be made. While its occurrence is rare, cases have been reported by different men, the conclusions being derived chiefly from the symptomatology, Wassermann test, roentgenologic examination, and therapeutic results. There is considerable opportunity for argument in accepting the aforementioned data as evidence of specificity in the absence of postmortem examination and microscopic demonstration of the spirochetes; however, many other facts of medicine are freely accepted on less authenticity.

However, the presumption that syphilis may affect any organ or tissue in the body, and the increasing case reports of syphilis of the stomach, strongly support, not only the fact of its existence, but a more frequent occurrence than is generally recognized.

The symptoms are not sufficiently characteristic so as to recognize it without the aid of laboratory methods. Achylia has been observed in a large percentage of cases. The roentgenologic manifestations of gastric lues are not characteristic, although in the ulcerative and hyperplastic types the roentgen signs are well marked. Organic hour-glass contraction is the principal sign.

Niche is usually absent. If the process goes on to extensive infiltration, or sclerosis, the roentgen evidence is more pronounced. Gastric deformity is obvious, this may be associated with decrease in size of stomach, dilatation of esophagus, lessened flexibility and mobility of gastric walls, absent or marked diminution of peristalsis and gaping or obstruction of the pylorus.

Usually the examiner considers malignancy first, but on due consideration will note the discrepancy between the extent of the lesion and the general condition of the patient, who is often under the cancer age; is anemic rather than cachetic; and is not markedly weakened or emaciated. When these signs are present and lues is suspected or possibly other luetic manifestations are observed elsewhere, the final diagnosis will have to be supplemented by laboratory and therapeutic tests for syphilis.

THE DIAGNOSTIC VALUE OF LOWERED BONE CONDUCTION IN SYPHILIS

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VARIOUS writers have called attention to the importance in the diagnosis of syphilis of a test based on the difference in the perception of sound conducted through bone as compared with an otherwise normal hearing test. The present study was made not only for the purpose of studying the reliability of such a procedure as an aid in diagnosing syphilis, but also to compare its efficiency with other means of recognizing the disease.

Extensive studies have been made on the syphilitic involvement of the eighth nerve, and on lowered bone conduction in syphilis, but methods and interpretations have differed materially from ours. Our investigation was suggested to us by the work of Oscar Beck, Wanner, and Willcutt, who had, however, confined their observations largely to cases in the early stages of the disease. Wanner was able to make a diagnosis of syphilis in 95 per cent of the cases he examined, before the appearance of general symptoms. The diagnosis was later confirmed by positive Wassermann reactions and other characteristic findings. Beck's examinations were made largely in early cases, but he had occasion incidentally to examine a limited number of patients with varied manifestations in all stages of the disease. In Beck's cases, the phenomenon proved to be positive in the primary stage in only a few instances, and he believes that it manifests itself after the infection changes from a local to a constitutional one. Some of his florid eruptive cases gave a negative test. He contends, on the basis of his investigations, that the test is reliable in a high percentage of cases. Willcutt, on the basis of 293 cases of syphilis, most of them in the primary and secondary stages, with a few latent cases, subscribes to the value of the lowered bone conduction test.

The method employed in our observations was as follows: Hearing tests were done routinely by the otologist (Barlow) in a number of cases in which he was unaware of the diagnosis, and 100 cases were then selected in which the data were sufficiently complete to establish or exclude the presence of syphilis.

THE LOWERED BONE CONDUCTION TEST

The technic of the hearing test is not at all complicated and does not necessarily require special otologic training. Three tuning forks are necessary; one the vibration rate of which is 128 per second, one 256, and the third 2048. The forks are set in vibration either by stroking rather vigorously, or by striking the fork on the knee or on the palm of the hand. The examiner holds the fork close to the ear of the patient until the patient no longer hears the sound. The examiner, taking his own hearing for normal then carries the fork to his own ear to ascertain the patient's discrepancy, if any, and expresses in seconds, the difference between the time the patient hears the fork and his own hearing of it.

Part 1.—After examining the ears of the patient for other pathologic conditions, the 128 fork is set in vibration and is placed on the vertex of the skull of the patient, equidistant from the ears, and note is made of the equality of the tone as heard in both ears. Should there be a marked difference between the two ears, this must naturally be taken into account in any further examination and in the final interpretation. This test is known as the Weber test.

Part 2.—The fork used in the first test is set in rapid vibration, but this time it is simply held near the ear of the patient until he no longer hears it. The number of seconds that the patient hears the fork is noted. The examiner thereupon listens to the fork himself, noting the number of seconds that he hears it. Both ears are tested in this way giving the value of the low limit. The 2048 fork is then used in like manner giving the high limit of the patient's hearing.

Part 3.—This is the most important phase of the test; the comparison of the conduction of sound through bone in the patient, as compared with that in the examiner. The 256 fork is set in vibration by striking smartly against the palm of the hand, and the stem of the fork is held firmly to the mastoid process about the level of the superior margin of the external canal, and just behind the ear. The patient is asked to note carefully when he no longer detects the tone of the fork, at which time the examiner conveys the fork to a corresponding position on his own mastoid and carefully observes whether he hears the fork longer than the patient and if so, how much longer. The number of seconds the operator hears the fork after the patient ceases to hear it, is expressed in terms of the patient's deficiency as minus seven seconds or minus eight seconds, or whatever the numerical value may be found to be. If the patient hears the fork through bone longer than the examiner he has an increased bone conduction, which is designated as plus whatever the number of seconds may be. If the patient does not hear the fork as long as the examiner the patient's bone conduction is said to be decreased or lowered. This test is performed on both ears and constitutes the Schwabach test.

Part 4.—The Rinné test is next done which consists of comparing the conduction of sound by bone in the patient with his air conduction. This is obtained by holding the fork opposite the patient's external meatus after he has ceased to hear the sound through the bone. This test is essential to classify the type of deafness if any be present. Normal hearing shows air conduction of longer duration than bone conduction and is called a positive Rinné test. The acuity of hearing may be tested for whispered voice, but this is not essential as the bone conduction test is a tuning fork test.

If the examination of the ear does not show a pre-existent lesion, such as chronic suppurative otitis; if the high and low limits of the patient are normal, the perception of sound is about equal in both ears, and the Rinné is positive, but the bone conduction shows a decrease of five seconds or more, or is decreased out of proportion* to the rest of the fork tests, the patient is said to have a bone conduction sufficiently reduced in the presence of normal hearing to justify the assumption that he has syphilis. A decrease of four seconds is considered to be within normal limits because it has been found that there is a physiologic discrepancy between the actual interpretation and perception of the sound. By repeated tests on the same person, one of us (Barlow) found that the person becomes educated to interpret more accurately the vibration of the fork, and that a person at first showing a reduction of four seconds, by repeated trials and after overcoming his first nervousness will very often show practically no reduction.

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*A hearing test showing Rinné positive, the 128 fork reduced fourteen seconds, high limits or the 2048 fork reduced seven seconds and bone conduction reduced six seconds would not be indicative of syphilis because the bone conduction is not lowered out of proportion to the rest of the hearing test. Such a result indicates a true nerve or internal ear deafness. In a hearing test showing Rinné positive, low limits or the 128 fork reduced fourteen seconds, high limit or the 2048 fork reduced six seconds, but the bone conduction reduced ten seconds, we are justified in considering this test indicative of syphilis because the bone conduction is lowered out of proportion to the rest of the test.

In the carrying out of these tests, the patients were always examined in the same room, with the same set of tuning forks, about the same time of day, and by the same otologist. The perceptive power of the patient was also considered.

CLINICAL METHODS EMPLOYED

The diagnosis of syphilis was established or excluded by an investigation as follows:

1. *History.*—The history was taken in considerable detail, since it has been our experience that important points such as the presence in the past of a suggestive eruption, a persistent sore throat or mouth, falling of the hair, the taking of Wassermann tests previous to present examination, etc., are frequently overlooked in a routine or hasty clinical history.

2. *Residual Signs of Syphilis.*—A special effort was made to include details frequently slighted in routine examinations. Suspicious scars on the skin and mucous membranes were searched for. Solitary nodular, and infiltrative syphilitic recurrences on the skin were not overlooked. The presence of leucoplakia buccalis was considered a diagnostic aid, but the fact that this lesion may be of other than syphilitic origin was kept in mind. A perforated septum was regarded as significant. That this condition is not exclusively luetic was not, however, forgotten. Investigation for evidence of syphilis by neurologic examination, and by identifying old cardiac and vascular lesions, etc., was carried out whenever any doubt arose. Examination of the fundus of the eye was made in many cases for signs of old or recent syphilis in the form of chorioretinitis, perivasculitis, and primary optic atrophy.

3. *Laboratory Tests.*—The laboratory tests included, of course, the Wassermann and the provocative Wassermann tests, following the technic described by Stokes and O'Leary. In all cases presenting symptoms suggestive of central nervous system involvement a complete examination of the cerebrospinal fluid was made. Patients with

suspicious but not conclusive evidence of lues were given the benefit of a therapeutic test. This consisted in the administration of at least three doses of arsphenamine at weekly intervals, and usually about five injections of one-sixth of a grain of mercury succinimide per week, for from fifteen to twenty doses. An equivalent of the latter in mercurial inunctions was frequently employed.

We compared, in our 100 cases, (1) negative bone conduction results with negative syphilitic findings, (2) negative bone conduction results with positive syphilitic findings, (3) positive bone conduction results with negative syphilitic findings, and (4) positive bone conduction results with positive syphilitic findings. We then compared the individual symptoms and signs in the known syphilitic cases with the bone conduction findings, in order to detect any striking correspondence between the ear tests, and the luetic symptomatology. This comparison included: (1) an estimate of the value of bone conduction results in various types of early syphilis (chancre, secondary eruptive manifestations, etc.) (2) comparison of bone conduction results with the positive Wassermann in latent lues, (3) comparison of bone conduction results with diagnostic evidence of syphilis in the nervous system, (4) comparison of bone conduction results with diagnostic evidence of late cutaneous syphilis, (5) comparison of bone conduction results with diagnostic evidence of osseous syphilis and (6) comparison of the positive and negative Wassermann findings throughout the series with the results of bone conduction tests.

STATEMENT OF RESULTS

Positive bone conduction tests (reduction of five seconds or more with normal hearing), corresponded to positive symptoms and signs of syphilis in 100 cases taken at random in 46 per cent, when syphilis was actually present in 59 per cent. This gives the positive test an efficiency in known syphilis, of 78 per cent. The negative bone conduction tests (reduction of four seconds or less) under the same conditions corresponded to the clinical absence of syphilis in 21 per cent of the cases when syphilis was actually absent in 41 per cent. This gives the negative test an efficiency of 51.2 per cent in ruling out syphilis. This result compares very favorably with the accuracy of the Wassermann test, in the types of cases considered. The margin of error in the test as a routine diagnostic aid is indicated by the fact that in 20 per cent of the cases in which the bone conduction was reduced sufficiently to justify a suspicion of syphilis, no syphilis could be demonstrated, and in 13 per cent of cases in which syphilis was present, the bone conduction was negative and contributed nothing to the diagnosis.

Table I

AGREEMENT BETWEEN THE TEST AND OTHER CLINICAL AND LABORATORY SIGNS IN 100 ROUTINE MISCELLANEOUS CASES			
Bone conduction positive Syphilis present	46 per cent	Bone conduction negative Syphilis absent	21 per cent
DISAGREEMENT BETWEEN THE TEST AND OTHER CLINICAL AND LABORATORY SIGNS IN 100 ROUTINE MISCELLANEOUS CASES			
Bone conduction negative Syphilis present	13 per cent	Bone conduction positive Syphilis absent	20 per cent

In the early local, or primary, and the disseminate or secondary stages, the bone conduction test was unreliable since the number of cases of any given type dealt with was too small to yield trustworthy results. In some instances there was an eruption and in others there was none. Of six early cases, three showed a sufficiently reduced bone conduction for a diagnosis and three did not.

In comparing the results of the lowered bone conduction test with the Wassermann test in latent lues, it was interesting to note that the two tests corresponded in 80 per cent of our cases. There were fifteen of this type with a definitely positive Wassermann test and other evidence of syphilis; twelve of these cases showed a sufficiently reduced bone conduction, three did not.

In cases presenting syphilitic involvement of the central nervous system the test also proved equally reliable. Twelve of the fifteen patients studied showed a lowered bone conduction of five seconds or more. Of the remaining three, two showed a bone conduction four seconds below normal and one a lowered conduction of three seconds. It may be mentioned that the patient with a three seconds' reduction had been subjected to unusually efficient treatment.

All of six patients with late syphilis of the skin, showed a bone conduction lowered sufficiently to suggest syphilis. In all of these the Wassermann reaction was negative. We feel that in this type of case a larger group might reveal interesting findings, showing the value of the bone conduction test in suggesting the presence of syphilis even with a negative Wassermann test. It is granted, of course, that in cutaneous syphilis the test is of less value than in many other forms of syphilis because the morphology of the lesion is often sufficient for a diagnosis.

In patients with syphilitic bone lesions the test proved unreliable. There were seven in this group. In four of these the bone conduction was negative (not sufficiently lowered) and in three it was positive. In several of the negative cases the tests were made repeatedly, and always gave the same result. Why, in this type of case, the test should not have had a greater value, it is, of course, impossible to state at the present time.

Ninety-four patients were subjected to both a bone conduction test and a Wassermann test.* Of fifty-five patients with syphilis both tests were positive in nineteen. In six instances the Wassermann was positive and the bone conduction test was negative; in seven both tests were negative, and in twenty-three the Wassermann test was negative and the bone conduction test was positive. The test would thus appear to be an important aid in the recognition of syphilis which is Wassermann negative by the technic used, were it not for the margin of error represented by the frequency of the positive bone conduction test in the absence of syphilis.

Of thirty-nine cases in which syphilis was absent, its absence was confirmed in nineteen (4.7 per cent) by both a negative Wassermann and a negative bone conduction test. In no case in which syphilis was absent did both tests prove positive. It seems, therefore, that a negative Wassermann and a negative bone conduction test is fairly satisfactory evidence of the absence of syphilis. The bone conduction test was positive and the Wassermann test was negative also in nineteen cases in which syphilis was absent, an error of 48.7 per cent as contrasted with an effectiveness of 78 per cent. In other words, the test has little routine diagnostic value taken alone, since 78 per cent of positives in syphilitics is discounted by 48 per cent of positives in nonsyphilitics.

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*The routine Wassermann technic of the Clinic, carried out under the direction of Sanford, employs one Noguchi antigen and a rabbit-human hemolytic system, guinea-pig complement, and fresh, active patient's serum, with the usual controls. When more than one antigen was employed, two alcoholic extracts of syphilitic liver, a stock Noguchi antigen, and an alcoholic antigen, reinforced with 0.4 per cent cholesterin, were employed.

TABLE II

SYPHILIS PRESENT IN 55 CASES			
Bone conduction positive Wassermann positive	19 cases 34.6 per cent	Bone conduction negative Wassermann negative	7 cases 12.7 per cent
Bone conduction positive Wassermann negative	23 cases 41.8 per cent	Bone conduction negative Wassermann positive	6 cases 0.9 per cent
SYPHILIS ABSENT IN 39 CASES			
Bone conduction positive Wassermann positive	0 cases 0 per cent	Bone conduction negative Wassermann negative	19 cases 48.7 per cent
Bone conduction positive Wassermann negative	19 cases 48.7 per cent	Bone conduction negative Wassermann positive	1 case 2.6 per cent

CONCLUSIONS

1. The so-called lowered bone conduction test (reduction in conduction of sound by bone as compared with otherwise normal hearing) is positive in 78 per cent of known syphilitics in our series.

2. From the otologic standpoint the test is only of value if a complete hearing test is done.

3. The efficiency of the test varied greatly in different types of syphilis, being at its best in late cutaneous syphilis (100 per cent), latent syphilis (80 per cent), syphilis of the central nervous system (80 per cent). It had almost no value in osseous lues, and the results in early syphilis were inconclusive (too few cases). A negative Wassermann test combined with a negative bone conduction test is strong evidence of the absence of syphilis.

4. The test agrees with the positive or negative diagnosis of syphilis in 67 per cent, and disagrees in 33 per cent.

5. The test was also positive in 48.7 per cent of patients in whom syphilis could apparently be excluded.

6. It has, on the whole, therefore, only a restricted value as a diagnostic aid, owing to its high factor of error.

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CHOLESTERINIZED ALCOHOLIC EXTRACT OF HUMAN HEART AS AN ANTIGEN IN COMPLEMENT-FIXATION TEST FOR SYPHILIS

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THE question of the value of cholesterin reinforced alcoholic extract of human heart as an antigen in the complement-fixation test for syphilis has been debated for some time.

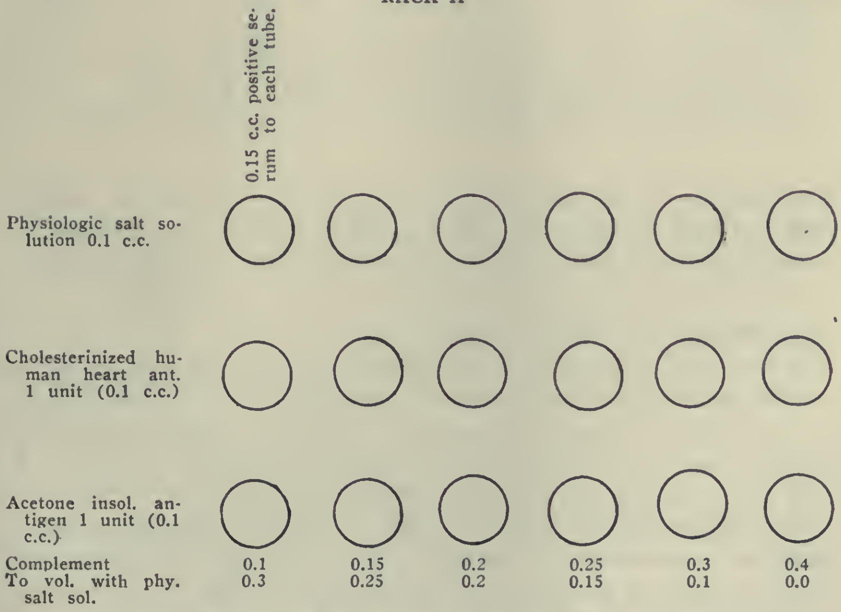
My purpose is to set forth some figures based on my experience with this antigen for a year ending several months ago, during which time I used it in 5787 tests. In all cases it was controlled by an antigen less sensitive, namely the acetone insoluble lipoid of beef heart.

A number of laboratory workers have mentioned the danger of false positive reactions when the cholesterinized antigen is used. Most of them have said nothing as to the degree of inhibition in these instances. I have found that cholesterinized antigen has a slight antihemolytic tendency; and in some cases where syphilis is not present, a slight degree of inhibition, 10 per cent or less, will sometimes occur. By some workers this is called positive, but this antihemolytic tendency of the cholesterin antigen is quite readily overcome and the danger of incorrect results or incorrect interpretation of results eliminated by an accurate titration of the complement against the antigen. In all of our tests the complement was titrated, using each antigen with a positive and with a negative serum. I have found that it is nearly always necessary to use for a unit of complement a slightly larger amount in the tube containing the cholesterinized antigen than in the acetone and control tube. Our titration of complement is carried out as follows:

Five healthy guinea pigs are selected and about 5 or 6 c.c. of blood withdrawn from each by cardiac puncture. The blood is transferred to centrifuge tubes, permitted to clot, and to remain in the ice chest overnight, the serum separating out. It should never be more than 12 to 18 hours old when used. On the day of the test, the serum from all guinea pigs is pooled, diluted to one in ten parts of physiologic salt solution (0.85 per cent), and titrated as follows:

Three rows of 6 tubes each are placed in 2 racks labeled "A" and "B" respectively. To each tube in rack *A* (Fig. 1) 0.15 c.c. of known positive serum is added. To each tube in rack *B* (Fig. 2) 0.15 c.c. of known negative serum is added. To each tube in both *A* and *B* racks in the first or front row one unit of acetone insoluble antigen is added. To row 2, or the middle row, one unit of cholesterinized human heart antigen is added. To the third or back row an equal volume of physiologic salt solution is added. To Series 1, 0.1 c.c. of complement is added; to Series 2, 0.15 c.c. is added; to Series 3, 0.2 c.c.; to Series 4, 0.25 c.c.; to Series 5, 0.3 c.c.; to Series 6, 0.4 c.c.; and all brought to the volume of the maximum amount, which is 0.4 c.c. with physiologic salt solution, and incubated for a half-hour in water-bath at 40° C. Two units of amboceptor and 0.5 c.c. of a 2 per cent suspension of washed sheep corpuscles are added. Again

RACK A

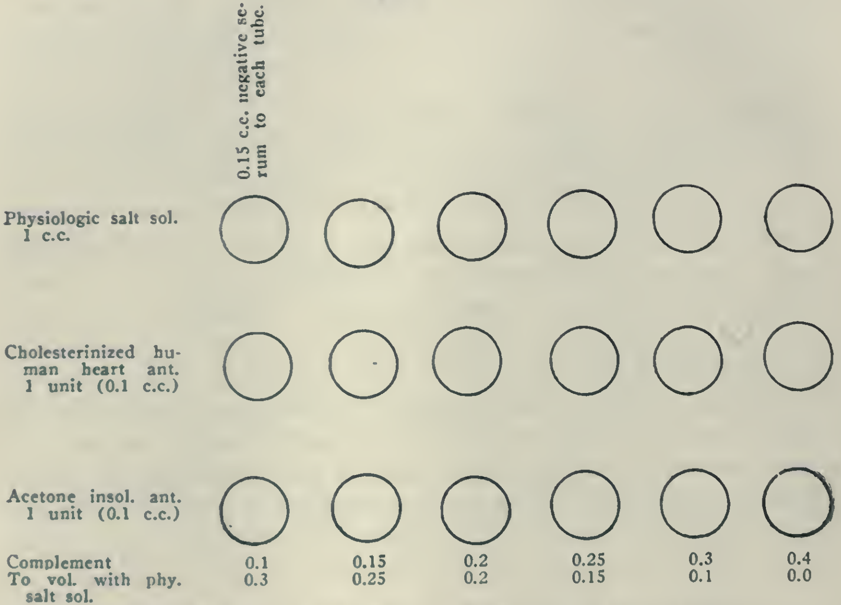

0.15 c.c. positive serum to each tube.
Physiologic salt solution 0.1 c.c.
Cholesterinized human heart ant. 1 unit (0.1 c.c.)
Acetone insol. antigen 1 unit (0.1 c.c.)
Complement
To vol. with phy. salt sol.
0.1
0.3
0.15
0.25
0.2
0.2
0.25
0.15
0.3
0.1
0.4
0.0

INCUBATE at 40° C. FOR THIRTY MINUTES IN WATER-BATH.

Amboceptor 2 units } to each tube. INCUBATE FOR THIRTY MINUTES.
Sheep cells 1 unit }

Fig. 1

RACK B


0.15 c.c. negative serum to each tube.
Physiologic salt sol. 1 c.c.
Cholesterinized human heart ant. 1 unit (0.1 c.c.)
Acetone insol. ant. 1 unit (0.1 c.c.)
Complement
To vol. with phy. salt sol.
0.1
0.3
0.15
0.25
0.2
0.2
0.25
0.15
0.3
0.1
0.4
0.0

INCUBATE at 40° C. FOR THIRTY MINUTES IN WATER-BATH.

Amboceptor 2 units
Sheep cells 1 unit } to each tube. INCUBATE FOR THIRTY MINUTES.

UNIT—Smallest amount which produces hemolysis with negative serum.

Fig. 2.

incubated for a half-hour at 40° C. in a water-bath and reading made. The point at which hemolysis is complete with the negative serum is taken as the unit, the corresponding tube of positive serum, in which a like amount of complement was used, serving to act as a guard against an excess of complement.

In the case of the acetone, we usually find the amount necessary to lake the cells in the presence of negative serum to be 0.05 to 0.1 c.c. less than the amount necessary to produce complete hemolysis with the cholesterinized antigen, thus demonstrating a slight tendency on the part of the cholesterin to inhibit hemolysis.

In carrying out the main test with the unknown serum of a number of patients, we would, therefore, use as our unit the amount necessary to produce hemolysis with each antigen in the negative series.

In the series of 5787 cases examined there were 47 instances in which the antigens disagreed in their result. I was able to obtain complete records in 39 of these.

In the 39 instances:

35—Definite history and symptoms of syphilis from 1 to 37 years ago.
2—Probable.
1—Doubtful.
1—Patient from India. Gave negative history relative to syphilis, but positive to malaria.

In 33 of the 35 cases with definite history and symptoms, the acetone antigen was completely negative. In one of the remaining two the acetone antigen was one-plus, showing less than 50 per cent inhibition, and in the other the acetone antigen was two-plus, showing 50 to 75 per cent inhibition.

In the cases above-named the test was done for diagnostic purposes. Therefore, if cholesterinized antigen had not been used, 33 of the 39 patients would have been given a clean bill of health, whereas the cholesterin-reinforced product was able to detect the presence of syphilitic antibodies, and treatment was instituted.

It is in the control of treatment that we find the greatest value of the cholesterin antigen, because it remains "positive" for a considerable length of time after the acetone has cleared up. In many such instances an examination of the spinal fluid reveals the presence of syphilitic antibodies.

CONCLUSION

1. Cholesterinized alcoholic human heart extract is probably the most sensitive antigen used in the complement-fixation test for syphilis.

2. In a small number of tests, its use results in a slight degree (10 per cent or less) of inhibition, in cases not syphilitic.

3. This antihemolytic tendency can be overcome by proper titration of complement.

4. Cholesterinized human heart antigen should never be used alone, but controlled by an antigen less sensitive.

5. It is especially valuable in the control of treatment, remaining positive for a considerable length of time after all other antigens are negative.

THE "PROVOCATIVE" WASSERMANN TEST

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(Received for publication, March 21, 1919)

THE data on which this paper is based were collected and the results of the study established more than two years ago. Numerous incidents beyond our control have delayed publication.

The theory of the provocative arsphenamine injection is briefly as follows: in the normal course of a syphilis or as the result of treatment the number of spirochetes or their function may be so reduced that certain products of their activity, the "Wassermann body,"—which following Neisser we shall call "reagen"—may be entirely absent in the blood of the infected individual or be present in a quantity too minute for detection by the Wassermann test. This assumption is, of course, correct; it is proved by the reversal of the Wassermann-negative to a positive after a period of therapeutic rest in early cases and by the occasional occurrence of a negative reaction in cases with obvious lesions in the later stages. If, in this Wassermann-negative stage of the infection, a small—therapeutically inadequate—amount of arsphenamine is injected into the patient, the theory assumes, the spirochetes present in the system will be provoked temporarily to greater functional activity, with the result that an amount of reagen will be formed great enough to yield a positive reaction with the Wassermann test.

The importance of a test for the determination of the disappearance of the last spirochete from the infected host can not be overestimated and the "provocative" Wassermann test seemed as great a boon from the therapeutic and prognostic standpoint as the Wassermann reaction itself from the point of view of diagnosis. A means of answering definitely the unhappy syphilitic's question "When may I stop treatment and feel safe?" was welcomed by the clinician as of the greatest value.

The test was used furthermore for diagnostic purposes; in obscure cases suspected to be luetic the "provocative" test was employed to bring about a positive reaction where before the reaction had been negative, thus establishing the diagnosis.

Unfortunately it was not long after the "provocative" test had been introduced and advocated as a procedure which must necessarily precede the discharge of the syphilitic from treatment, that various observers began to have doubts of its efficacy. At the annual meeting of the American Dermatological Association in May, 1916, one of us reported that he was still employing the "provocative" test in deference to prevailing opinions, but that he was not at all sure of its value, and that an investigation (of which this paper is the outcome) was then under way.[1] Since that time several publications have appeared unfavorably criticizing the "provocative" test, but a considerable number of clinicians are still making use of the test and within the past month one of our leading syphilologists publicly expressed the opinion that no syphilitic should be regarded as cured until he had been proved so by the negative Wassermann reaction following a "provocative" injection of arsphenamine.

Unlike Stokes[2] who confined his inquiry to cases of doubtful diagnosis using the "provocative" test for diagnosis only, our work was directed to the question of determining whether in cases of known syphilis the test could be relied on as a test of cure. It may be stated here that Stokes concluded that as a diagnostic test the "provocative" injection does not equal the old therapeutic test in reliability.

In the course of this investigation the "provocative" test was made in about 150 cases of syphilis that had become Wassermann negative after treatment. For the most part an intravenous injection of 0.2 gram arsphenamine was given and blood drawn for the Wassermann test on the following day and again at two days' interval for eight days and twice during the succeeding week; indicating the day of the injection as day 0, the Wassermann specimens as taken on days 1, 3, 5, 7, 10 and 15. This rule was not followed invariably but prevailed in certainly three-quarters of the cases. The Wassermann reactions were tested in the laboratory in one of the leading general hospitals of this city where the work was under the supervision of a former pupil of Citron (Wassermann's assistant). The work of this laboratory may be regarded as at least as reliable as that of the average serologic laboratory. The antigen used was generally alcoholic extract of guinea pig's heart. Certain irregularities in the reports of the Wassermann tests led us to make them in duplicate in about one-third of the cases. We desire to express here our obligation to Mr. Koopman of the New York Health Department's Wassermann

Laboratory for his generous cooperation in this work. In the Health Department's Laboratory both simple alcoholic extract and cholesterinized antigens were employed.

1. Our reason for undertaking a series of these Wassermann tests in duplicate and in different laboratories lies at the very bottom of one of the great objections to the "provocative" test, namely, the unreliability of the Wassermann test *per se*. No one who has had a large experience with the Wassermann test, who has, so to speak, stood between the patient and the laboratory correlating the clinical with the laboratory evidence in a large series of cases, would deny the great value of the Wassermann test for the clinician; but no one with any considerable experience would be willing to accept a single Wassermann report, in the absence of supporting clinical data, as conclusive evidence either for or against the presence of a syphilitic infection. Every clinician has again and again received Wassermann reports in obvious contradiction to the unquestionable evidence. One of us can point to at least a score of cases of untreated syphilis with florid eruptions in the secondary stage in which a laboratory reported the Wassermann reaction negative; and this not from one laboratory, the quality of whose work would thereby be greatly impugned, but from many laboratories in different parts of the country.

It is not our purpose to discuss the causes of these variations or errors; they have been recorded by numerous observers. Whether the considerable variations in the intensity of the reactions in a series of tests on blood from the same individual depend on undetermined differences in the blood itself or in the reagents, the fact is that the results of the tests may be misleading as an index of the presence or absence of syphilis. Craig's[3] work on these variations may be referred to. These differences are undoubtedly in part the result of accidents in the laboratory. In a fairly complicated chemical test involving many steps, the human factor necessarily plays a role. The negative Wassermann reactions reported, for instance, in cases of florid syphilis are due to an error in some step in the laboratory or sometimes to an error in the records, such as misplacing the labels on the tubes; but whatever the cause the fact is that any given Wassermann report may be flatly wrong or be misleading for reasons at present inseparable from the test.

To illustrate from one of our cases:

A. X. had been long and well treated for an infection more than eight years old when, after 18 months of negative Wassermann reactions without treatment, a "provocative" test was made. The reports came as follows:

Day	0	1	2	4	6	8	14
W.R.	0	0	0	4+	0	0	0

These reports show a strong positive reaction on the fourth day; but a moment's consideration will lead to the conclusion that the 4+ report on that day is an error. A four-plus reaction implies a large amount of reagen in the blood, which, it is true, might have developed rather abruptly between the second and the fourth day; but all our experience with syphilis contradicts the idea that the reagen is rapidly eliminated. A four-plus Wassermann would probably require at least a fortnight to become negative even when no fresh reagen is being produced. The Wassermann curve, in other words, would be a gradually declining one; from four-plus on the fourth day it might decline to a three-plus on the sixth day, two-plus on the eighth, + to ± or negative a week or two later. This case with apparently strong response to a "provocative" injection when analyzed leads to the conclusion that the report is wrong. As a matter of good fortune, sufficient unused serum from the specimen of the fourth day was found in the laboratory and when the test was repeated with this serum the reaction was found to be negative.

Our first point is that the Wassermann is too uncertain in its results to justify us in trusting to it so important, so vital a conclusion as the cure of syphilis.

2. In one of our cases in whom the Wassermann reaction was found negative for a year without treatment, the patient was directed to report the following week for a "provocative" injection. He failed to return as directed, but reported to us a month later. Before proceeding with the injection we made another Wassermann test and found it positive.

If this man had received his "provocative" injection without the preliminary blood test, we might have concluded from the succeeding tests, made after the injection, that we had a clear case of a "provoked" reaction. We have no doubt that this error has frequently occurred; in our series we had six cases of this kind. The Wassermann reaction may become positive in an uncured Wassermann negative syphilitic at any moment, and it is possible, of course, for the change of phase to occur just about the time the "provocative" injection is given. We admit the probabilities are greatly against this coincidence in any one case, but the possibility must always be reckoned with. We made it a rule after our experience invariably to take a specimen of blood for a Wassermann test immediately before giving the "provocative" injection..

3. In our entire series of 150 cases of Wassermann negative syphilitics we did not find a single clear case of a provoked reaction.

There were, it is true, a few cases that may have been interpreted as showing a provoked reaction, but without exception they presented some irregularity that negatived the value of the test. For instance:

W. S. Syphilis III, asymptomatic, Wassermann negative; "provocative" injection, June 12, 1916.

Day	0	1	2	3	5	9	30	90	
W.R.	0	2+	±	0	0	+	2+	2+	(alcoholic antigen)

Apparently a good case of a "provocative" reaction! But this case tested in duplicate with the cholesterinized antigen gave the following result:

Day	0	1	2	3	5	
W.R.	+	+	+	+	+	(cholesterinized antigen.)

What interpretation we ask could possibly be placed on these reactions?

To take another case:

J. O. Syphilis III, asymptomatic, negative 14 months without treatment after several years of arsphenamine and mercury.

Day	0	1	3	5	12	36	60	90	150
W.R.	0	0	0	±	0	0	0	0	2+

Whoever is willing to regard this as a positive result in a provocative test is welcome to do so; for our part we believe that no attention need be paid to a single plus-minus reaction occurring five days after injection This patient became definitely positive, however, five months later.

A. K. Syphilis III, asymptomatic Wassermann negative.

Day	0	1	3	4	25	32	37	50	80	100	107
W.R.	0	0	0	0	2+	+	0	0	±	+	3+

No "provocative" reaction, but strongly positive six months later. The two-plus occurring on the twenty-fifth day might be interpreted by the "provocative" enthusiasts as a "delayed reaction" but it seems to us rather to illustrate Craig's point of fluctuations in the Wassermann in a series of tests in a syphilitic.

With the exception of perhaps half a dozen cases of the above character which might possibly, by straining the probabilities, have been interpreted as "provocative" reactions, we had not, we repeat, a single clear-cut case of a "provocative" reaction in our syphilitics.

4. It is obvious that as our tests were made in cases that had for the most part been long under treatment and were clinically and serologically negative, our failure to obtain a positive after the "provocative" injection might be due to the fact that most of our patients were really cured of their disease and might, therefore, be regarded as a tribute to the excellence of our treatment. We are frank to admit that we laid no such flattering unction to our souls. To test the question we selected a number of patients in any early stage of their disease, who, though Wassermann negative after one or two courses of treatment, were in all probability not cured. These seemed to us to offer ideal conditions for a trial of the value of the "provocative" injection as a test of cure. These cases, we assumed, and in most of them the assumption was subsequently proved to be correct, while temporarily Wassermann negative, still harbored spirochetes though too few in number or too inactive to cause the production of a sufficient quantity of reagen to give a positive Wassermann reaction. If the theory underlying the "provocative" Wassermann test is correct, an injection of 0.2 arsphenamine must result in an increased production of reagen and a positive Wassermann reaction in these temporarily negative cases. We give a few of these cases in some detail:

S. L. Infection April, 1915, Wassermann negative April 5, 1916, after treatment. Provocative injection May 15, 1916.

Day	0	1	2	3	7	22	54
W.R.	0	0	0	0	0	0	4+

No "provocative;" but strong positive two months later.

J. L. Infection August, 1915, negative June 10, 1916, after treatment. Provocative July 28, 1916.

Day	0	1	2	3	12	33	47	77
W.R.	0	0	0	0	0	0	±	4+

No provocative; but strongly positive after two and one-half months.

J. F. Infection October, 1915, negative July 8, 1916, after treatment. Provocative July 31, 1916.

Day	0	1	2	3	5	12	26
W.R.	0	0	0	0	0	0	0

No provocative. Patient did not return until November 3, 1917, 15 months later, when he was found to be strongly positive.

E. S. Infection August, 1915, negative February 1, 1916, after treatment. Provocative February 28, 1916.

Day	0	1	3	5	12	22	29	38	74	90
W.R.	0	0	0	0	0	0	0	0	2+	4+

No provocative; but strongly positive after three months.

These examples are typical of the nine cases of this kind; uncured secondary syphilitics showing no reaction after the "provocative" test.

If, on the contrary, in one or two of our series of cases, a "provocative" injection had yielded a positive response, the uncertainties of the Wassermann reaction might well have left us in doubt as to the correctness of the conclusion that their syphilis was still present. But even if we were to assume that the Wassermann reaction is in every case a perfect and absolutely dependable test of the presence of syphilis, the fact that in the great preponderance of the cases (in our series in every case!) of temporarily negative syphilitics, the "provocative" injection failed to show the presence of syphilis completely invalidates the test. We might, it is true, be in a position to say that these one or two cases were not cured; but if we drew the contrary conclusion in the remaining cases trusting to the negative result of the "provocative" injection, we should be woefully wrong and by regarding these cases as cured, do our patients the greatest injury. The fact that some observers have reported five or ten or fifteen per cent of positives after the "provocative" test only serves to prove the unreliability of the test; and we doubt very much whether even the advocates of the test would trust in it sufficiently to lead them to discharge as cured the remaining large percentage of their cases.

To sum up:

1. The Wassermann test is so subject to errors of various kinds that dependence on a single positive reaction in a series of tests is not justified.

2. In an uncured case a change from a negative to a positive reaction may happen to coincide with the "provocative" injection and a positive found after the injection may be the result of the normal increase in reagen without relation to the injection.

3. In a series of about 150 cases of treated syphilis of all kinds we did not find a single clear case of a provoked reaction; while the assumption of a cure in all these cases is obviously untenable.

4. In a series of cases temporarily negative, selected as probably not cured, the "provocative" test failed to indicate the presence of syphilis though the subsequent course of the cases proved that the syphilis was not cured.

5. We regard the "provocative" arsphenamine injection as a useless and often misleading procedure.

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A SURVEY OF WASSERMANN REACTIONS MADE IN THE SEROLOGICAL LABORATORY OF THE CITY OF CLEVELAND

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IN this report I have undertaken to summarize the results of approximately 10,000 Wassermann tests made in the Serological Laboratory of the Division of Health of the City of Cleveland, during the period from Aug. 1, 1916, to Aug. 1, 1918. The facts are certainly interesting and enlightening as to the prevalence of syphilis in this city. Indeed, the problem of syphilis today is national and deserves more consideration than ever before. Although our fighting men have been guarded as no other soldiers were ever guarded against infection, it is a well-known fact that with every war there is a great increase in venereal disease incident upon the return of the forces. The public in general is as yet more or less inclined to disregard, or at least minimize, the threatening increase of this devastating disease.

During the month of June, 1918, sixty-four women inmates of the Work House at Warrensville were examined; of these, 29 gave a definite positive reaction, making the percentage 45. In the recent campaign against venereal disease in Ohio a raid was made on a few suspicious houses of Barberton. Fifteen women were arrested and examined. None of these showed clinical symptoms of the disease but the Wassermann test revealed eleven positives. These girls were engaged in prostitution for a period of from four months to two years.*

Kramer[1] examined 1583 out of the 1800 inmates in the Ohio penitentiary on July 1, 1915: 288, or 18.1 per cent, gave either positive or partial positive reactions. Of these 288, forty-three, or 14.9 per cent gave a clinical history. Of the colored population, 58, or 13.4 per cent, were positive, while 108, or 20.9 per cent, of the American-born population were positive. Similar studies on both men and women from penitentiaries were reported by Snow[2] with proportion of positives varying from 10 per cent up to 48 per cent. These facts certainly emphasize the crying need for venereal disease control of the population of institutions of this sort.

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*Dr. H. N. Cole has been so kind as to give me the results of these examinations.

The results of the laboratory examinations are not representative of the city at large, as our routine examinations only cover cases with a suspicious history, or with obscure symptoms. A systematic canvass of the city would undoubtedly reveal a somewhat lower percentage of positive reactions than we have obtained. A large series of cases had to be discarded because of insufficient records. The total number examined is 9412, of whom 7778 were classified according to occupation, marital condition, and sex. Comparatively few tests were made on the colored population of the city, the total number classified being 363.

Tables I and II present the percentage of syphilitics by age and sex as found at the serologic laboratory:

TABLE I

MALES BY AGES. TOTAL POSITIVES AND NEGATIVES

AGES	TOTAL NUMBER	TOTAL POS.	TOTAL NEG.	PER CENT POS.	PER CENT POS. OF GRAND TOTAL (6475)
0-5	219	34	185	15.52	0.53
6-15	87	12	75	13.79	0.19
16-25	1320	302	1018	22.73	4.67
26-40	3346	851	2495	25.44	13.14
41-60	1384	315	1069	22.76	4.86
61+	119	21	98	17.65	0.33
Total	6475	1535	4940	23.71	

From Tables I and II it is evident that the greatest incidence in both men and women occurs between the ages of twenty-six to forty. Between the ages sixteen to twenty-five the incidence is higher in females than in males owing to the earlier maturity of the former. The total percentage of positives found is slightly higher in females than in males. This is due to the larger number of male cases studied, or to the fact that more of the females tested showed suspicious symptoms. It is also interesting to note the decrease of posi-

TABLE II

FEMALES BY AGES. TOTAL POSITIVES AND NEGATIVES

AGES	TOTAL NUMBER	TOTAL POS.	TOTAL NEG.	PER CENT POS.	PER CENT POS. OF GRAND TOTAL (2937)
0-5	220	30	190	13.64	1.02
6-15	78	19	59	24.36	0.65
16-25	783	231	552	29.50	7.87
26-40	1306	349	957	26.72	11.88
41-60	500	103	397	20.60	3.51
61+	50	2	48	4.00	0.068
Total	2937	734	2203	24.99	

tives in the more advanced ages, forty-one and over. It seems probable that a large number of these cases were tertiary cases or cases which had received intensive treatments.

Vedder[3] found that the percentage of infections increases steadily with advancing years among presumably healthy men of the class that enlist in the army The increase is as follows: 18 to 22, 10 per cent; 23 to 27, 16 per cent; 28 to 32, 20 per cent; 33 to 37, 24 per cent; 38 to 41, 28 per cent. He believes that these figures indicate approximately the prevalence of syphilis among unmarried men of this class. The younger men will average below 20 per cent, but the older men will average more than 20 per cent; so that as a group it is probably fair to estimate a prevalence of 20 per cent. The group includes unskilled labor and certain percentage of trades. Among men from better families or who have received better education the percentage is much lower, probably varying between 2 and 10 per cent; depending upon age, marital condition, and other factors. Craig[4] believes that at least 15 per cent of all applicants for enlistment for the army, prior to the present war, were infected with syphilis, and this means that practically 15 per cent of the average male civilian population of this country between the ages of 20 to 30 are infected. From many surveys of presumably healthy women Vedder[5] estimates that among young women in the community the percentage of syphilitic infections fluctuates between 3 and 20 per cent; depending upon age, marital condition, education and social status. According to the same author the infection is rare among the unmarried girls of good character, but is only too common among married women whose virtue is beyond challenge. Fischer[6] estimates that 18 per cent of the population suffers from syphilis and that 250000 deaths occur each year as the result of venereal diseases.

Tables III and IV give married and single cases classified by occupation. .

TABLE III

MALES BY OCCUPATION. TOTAL POSITIVES AND NEGATIVES

OCCUPATION	MARRIED		PER CENT	SINGLE		PER CENT	PER CENT
	POS.	NEG.	POS.	POS.	NEG.	POS.	POS. OF GRAND TOTALS
Outdoor Laborers	234	836	21.87	214	655	24.62	23.11
Indoor Laborers	158	340	31.83	107	269	28.45	30.32
Mechanics	87	189	31.52	65	182	26.32	29.06
Salesmen (Trav.)	66	152	30.28	53	85	38.40	33.43
Clerks	40	137	22.60	56	116	32.55	27.50
Bartenders	11	13	45.84	9	20	31.03	37.62
Waiters	5	8	38.46	9	30	23.10	26.93
Professionals	21	48	30.44	12	46	20.69	25.99
Barbers	8	10	44.44	5	7	41.66	43.33
Seamen	18	48	27.28	75	245	23.44	24.09
Soldiers	5	2	71.43	5	26	16.13	26.32
Undetermined	134	450	22.94	144	462	23.76	23.35

TABLE IV

FEMALES BY OCCUPATION. TOTAL POSITIVES AND NEGATIVES

OCCUPATION	MARRIED		PER CENT	SINGLE		PER CENT	PER CENT
	POS.	NEG.	POS.	POS.	NEG.	POS.	POS. OF GRAND TOTALS
Domestics	420	1023	29.11	49	166	22.79	28.29
Professionals (teachers, artists, nurses, etc.)	11	12	47.83	8	35	18.61	28.80
Clerks (stenographers, saleswomen)	19	32	37.26	22	87	20.18	25.62
Waitresses	14	16	46.66	9	21	30.00	38.33
Seamstresses	4	10	28.57	3	4	42.86	33.33
Factory Workers	1	5	20.00	3	11	27.27	20.00
Undetermined	32	73	30.48	51	224	18.55	21.85

Among the males the largest number of tests were taken in the laboring classes, and a disproportionate small number among waiters, barbers, professionals and soldiers. It is interesting to note that the percentage of positives is higher among indoor laborers than among outdoor laborers. Similarly salesmen have a higher percentage than clerks, a fact which has been observed before. In general there was a slightly higher proportion of positives among the married males, and among married females the percentage was higher than among the single. The percentage of positives among housewives approximates 30. The total number of tests made on housewives is many times larger than that of the total of all other occupations.

Table V gives the total positives in married and single males and females.

TABLE V

TOTAL POSITIVES AND NEGATIVES IN MARRIED AND SINGLE MALES AND FEMALES

MARRIED		PER CENT	SINGLE		PER CENT
POS.	NEG.	POS.	POS.	NEG.	POS.
1249	3308	27.48	812	2409	25.21
Grand total of cases, 7778. Per cent positive, 26.49.					

Jamieson[7] in his article entitled "Syphilis in Detroit as an Economic and Social Factor," treats the subject in a different manner from that followed in this report. Still, his article and the present one are interesting to compare, as Detroit and Cleveland are both manufacturing cities with similar congestion, industrial and social problems. Jamieson finds 26.75 per cent marital infections while we find 27.48 per cent.

Table VI gives the total number of positives among the colored population subdivided into males and females, married and single.

TABLE VI

COLORED MALES. TOTAL POSITIVES AND NEGATIVES

MARRIED		PER CENT	SINGLE		PER CENT	PER CENT POS.
POS.	NEG.	POS.	POS.	NEG.	POS.	OF TOTALS
39	56	41.05	62	87	41.61	41.39
COLORED FEMALES. TOTAL POSITIVES AND NEGATIVES						
44	38	53.66	7	37	18.90	42.85
TOTALS						
83	94	46.89	69	117	37.09	
Grand total, 363. Per cent positives, 41.87.						

The total number examined is not sufficient to furnish very extensive information. It will be observed that the percentage of positives is considerably higher than in the case of the whites. The total percentage of positives was 41.05. McNeil[8] reported 34 per cent positives among sick negroes applying at clinics while the incidence among ostensibly healthy negroes was about 24 per cent. We may estimate that the rates for the colored race are double those for the white race and that the disease is even more common among negro women than among negro men.

SUMMARY

Of 9412 Wassermann tests made at the Serological Laboratory of the city of Cleveland (Ohio) during the last two years 6475 were male cases, and 2937 were female cases.

The percentage of positives among the males was 23.71 and among the females 24.99. The percentage of positives increased with advancing years, but decreased between the ages of forty-one and sixty. The percentage of positives among females between the ages of sixteen and twenty-five was considerably higher than that of the males of the same ages.

The largest number of tests were made among the laboring classes of the city. With exception of clerks and salesmen there was a larger percentage of positives among the married than among the single in the different occupations.

The percentage of positives among housewives was 29.11.

The incidence was considerably higher in the colored than in the white race. The percentage of positives among the married colored was 46.89 while among the married white 27.48. The percentage of positives among the single whites was 25.21 and among the single colored 37.09.

I wish to express my indebtedness to my wife and to Miss R. Davis for their valuable aid in the classification of the materials.

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THE COLLOIDAL GOLD REACTION

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THE first preparation of colloidal gold recorded was made by Faraday[1] in 1857. He reduced gold chloride with phosphorus and obtained fluids ranging from red to violet in color but which were quite unstable. The gold was precipitated when the fluid was boiled. In 1898 Zsigmondy[2] published the results of his work on colloidal gold. Solutions prepared by him were stable, were not affected by boiling and were very sensitive to the action of electrolytes. Very small amounts of gelatin, .0001 per cent, would appreciably protect the gold from the action of electrolytes. Other colloids were found that possessed this same protecting quality. This general property of protecting gold solutions possessed by many colloids, led Zsigmondy to measure the extent of their protecting properties quantitatively and to fix a gold number for each. By gold number is meant the number of milligrams of the colloid which is just sufficient to prevent the change to violet of 10 c.c. of bright red colloidal gold of a percentage .0053 by the addition of 1 c.c. of 10 per cent sodium chloride solution. He suggested that the protective action may be better expressed by the reciprocal of this number. The gold numbers of many proteins were determined and when established for any purified protein could later be used to determine the purity of a known protein, the amount of purified protein in a given solution and the nature of an unknown purified protein.

Much study had been given the proteins of the spinal fluid and Lange[3] attempted to determine their nature by making use of Zsigmondy's gold numbers. Spinal fluid was diluted with water, but it was found that this caused the globulins to precipitate. Later a .4 per cent sodium chloride solution was used. Such a solution would keep the globulins in solution and itself would not cause any change in the colloidal gold. Spinal fluids from paretics gave wholly unexpected results. It was observed that the fluid not only did not protect the gold but actually caused it to precipitate and in a constant and characteristic manner. Spinal fluids from tabetics and normal spinal fluids did not cause this reaction. Since Lange's paper was published, a number of observers have reported on the effects of spinal fluids on colloidal gold solutions. Reference will be made to these later.

PREPARATION OF COLLOIDAL GOLD

Lange prepared colloidal gold by adding to 1,000 c.c. of distilled water, 10 c.c. of a 1 per cent gold chloride solution and 10 c.c. of 2 per cent potassium carbonate solution and applied heat until the temperature of the mixture was 90° C. Ten c.c. of 1 per cent formalin were then added and the mixture stirred.

Miller and Levy,[4] Lee and Hinton,[5] Harvey,[6] Swalm and Mann,[7] Potter,[8] Weston, Darling and Newcomb[9] and others used the Lange technic in their work.

Eike[10] used 1,000 c.c. of distilled water, 5 c.c. of 5 per cent dextrose and 10 c.c. of 1 per cent gold chloride solution. This mixture was heated to 90-95° C. and then 5 per cent potassium carbonate solution was added drop by drop until the bright red color was produced. Oetiker[11] modified Eike's technic by adding at once to the heated mixture of gold chloride and dextrose 12 c.c. of 2 per cent potassium carbonate solution. Hulbert[12] made colloidal gold by bubbling formaldehyde gas through the gold chloride and potassium carbonate mixture. Miller, Brush, Hammers and Felton[13] had difficulty at times in making colloidal gold. With the same reagents and glassware, they were not always able to obtain good solutions. This was in accord with the experience of others. They studied the various factors involved and published the following method: to 1,000 c.c. of triply distilled water at 60° C. are added 10 c.c. of 1 per cent gold chloride solution and 7 c.c. of 2 per cent potassium carbonate solution. At 80° C., while stirring briskly, 10 drops of 1 per cent oxalic acid solution are added. At 90° C. the burner is removed and while the mixture is stirred, 5 c.c. of 1 to 40 formaldehyde or enough to produce an initial pink color are added. Black and Rosenberg[14] studied the effects of the alkali, formaldehyde and carbon dioxide and the influence of heating. Their technic is to add to 10 c.c. of 1 per cent gold chloride solution and 7 c.c. of 2 per cent potassium carbonate solution in 1,000 c.c. of water at incipient boiling, 5 c.c. of 1 per cent formalin, stirring until reduction is complete. Later directions by the same authors[15] call for 8 c.c. of the potassium carbonate solution and 1 c.c. of 1 per cent formalin. The last should be added at boiling temperature. Felton[16] studied the effect of varying the amounts of gold chloride, potassium carbonate and formaldehyde. He recommends 10 c.c. of 1 per cent gold chloride solution, 8 c.c. of 2 per cent potassium carbonate solution and 6 c.c. of 1 per cent formalin in 1,000 c.c. of distilled water. The first two reagents are added to the water and the mixture brought to a boil. The formalin is then added slowly until the color is almost complete and the remaining formalin is then thrown in. Stirring is unnecessary. Lee[17] gives the following technic: to 1,000 c.c. of distilled water, add 10 c.c. of 1 per cent gold chloride solution, 7 c.c. of 2 per cent potassium carbonate solution, 1.75 c.c. of 1 per cent oxalic acid solution and .83 c.c. of 1 to 40 formalin or equivalent of 8.07 milligrams of formaldehyde per liter. Mix, place over the burner and heat with occasional stirring to 80-85° C. Then reduce the flame enough to keep the temperature constant.

The author has used all the methods and like others has found that at times each method failed. Everything concerned in making the reagent has been accused of causing failure to make good solutions. Most workers agree that, given clean glassware, twice distilled water and pure reagents, good results are dependent on the proper temperature and the right amount of formalin. The technic of Miller, et al, is widely used and is very constant in its results. The method of Felton gives equally good results.

The finished reagent is sometimes found to be useless because it will not give reactions with paretic fluids. Solutions which gave typical reactions when used fresh, have been found not to do so after they are a few months old. They had become protected. Eskuchen[18] and Miller and Levy commented on this and later Miller, et al, studied the subject. They first observed that the gold could be completely precipitated from 5 c.c. of a nonprotected solution in one hour by the addition of 1.7 c.c. of 10 per cent sodium chloride solution. Alkaline solutions of gold were practically inert to the electrolytic forces of a positive spinal fluid and acid solutions gave a typical reaction with a paretic fluid, but also a very typical reaction in the luetic zone with a known negative fluid. A neutral solution gave the typical reactions with known paretic and luetic spinal fluids, but no change of color with a normal fluid. This last observation seemed to offer an explanation of protected solutions. By adjusting the reaction of a protected solution so that it is neutral, typical reactions can be obtained with paretic and luetic fluids. Normal fluids do not affect the color. Felton states that the hydrogen-ion concentration of 7, slightly more or less, is the most advisable reaction. By using the slit type ultra-microscope, he found that protected solutions gave a fairly dark field with few reddish particles while the nonprotected solutions gave a luminous field with a very great number of yellowish particles though both solutions contained the same amount of gold. He concludes tentatively that the protected solutions, excluding those protected by extraneous matter, are those of great dispersion and of too great surface area to be influenced by the precipitating agent of a paretic spinal fluid and it may be deduced from the statement given above that a colloidal solution of large ion-complexes makes precipitation possible and is most desirable for practical use.

The characteristics of a good gold solution may be stated as follows:

1. It must give a typical reaction with a known paretic fluid.
2. It must give no reaction greater than 1 with a known negative fluid.
3. It must be neutral at the time it is used.
4. It must be absolutely transparent, have an orange or red color and be wholly free from any trace of bluish tinge.

A fifth requirement is sometimes added; namely, the gold must be precipitated from 5 c.c. of the solution in one hour after the addition of 1.7 c.c. of 10 per cent sodium chloride solution. Colloidal gold answering all four of the requirements mentioned above answers all the conditions necessary for the test whether the gold is precipitated by the salt solution recommended or not.

TECHNIC OF THE TEST

Eleven test tubes are placed in a rack. The first receives 1.8 c.c. of .4 per cent sodium chloride solution and the other tubes 1 c.c. each. To the first tube is added .2 c.c. of the fresh spinal fluid to be examined and the pipette is thoroughly washed with the mixture. One c.c. is transferred to the second tube and mixed. One c.c. of this mixture is transferred to the third tube, and so on to the tenth tube. The extra c.c. in the tenth tube is discarded. To each tube is now added 5 c.c. of colloidal gold and each is thoroughly mixed. The result of the reaction can be read within an hour or even less time by one who is familiar with the test, but the tubes should stand at least twelve hours (overnight) before the final reading is made, and this can not be made very well with the usual artificial light.

The spinal fluid should preferably be perfectly fresh. This is not absolutely essential. Fluids kept under aseptic conditions in the ice box for one month gave the same gold and Wassermann reactions as when fresh. There is rarely any occasion to keep fluids for such a length of time before they are examined. Sterile spinal fluid kept in a sealed tube at room temperature for two years gave, when fresh, a typical paretic gold curve and a positive Wassermann reaction with one-tenth c.c. of fluid. At the end of two years, the Wassermann reaction was negative with 1.5 c.c. of fluid and the gold curve was typically luetic. Fluid drawn at the time of death or immediately after (within three hours) gives the same gold and Wassermann reactions as fresh fluid.

With paretic fluids a series of color changes will take place in the gold solution. To facilitate recording these colors, they have been given numbers as follows: complete precipitation of the gold with a clear, colorless, supernatant fluid is expressed as 5; pale or gray-blue, as 4; blue, as 3; lilac or purple, as 2; red-blue, as 1; and no change of color as 0. The color changes are so constant in some conditions that certain zones have been described.

1. The paretic zone. This term was introduced by Miller and Levy. In this zone the greatest reaction is in the first three to six tubes and is of the 5 type. The color values rapidly fall in the succeeding two or three tubes to 0.

2. The luetic zone. Here the greatest color change is in the fourth and fifth tubes but is never greater than 4 or less than 3.

3. The meningitic zone. The maximum color change occurs in the higher dilutions beginning with the sixth tube.

THE NATURE OF THE SUBSTANCE IN THE SPINAL FLUID CAUSING THE REACTION

Miller, et al, noticed that the gold precipitating substance was at least partially dialyzable. Matzkiewitsch[19] dialyzed 2.5 c.c. of paretic spinal fluid against 20 c.c. of distilled water for 16 hours in an incubator and found that the dialysate gave a strongly positive ninhydrin and gold sol reaction. No details of technic were given. Weston[20] using his own technic was unable to confirm the observation of Matzkiewitsch and attempted to determine the nature of the substance causing the precipitation of gold. He studied 30 paretic and 37 nonparetic (other psychoses) spinal fluids and found that the copper sulphate reducing substance, the Wassermann reacting substance, and the salts did not cause the precipitation of gold. The precipitating substance was dialyzable and was destroyed by boiling. It was not peptone as inferred by Matzkiewitsch. Felton studied the action of globulins and albumins on colloidal gold. The globulins were prepared by dialyzing spinal fluids in collodion sacs against distilled water at 42-44° C. Dialysis was continued until precipitation occurred and the time ranged from 10 to 100 hours. The water was changed every ten hours. After precipitation had occurred, the contents of the dialyzing sac were emptied into a centrifuge tube and the material centrifugalized. The precipitate was washed with distilled water and then dissolved in .84 per cent sodium chloride solution and made alkaline to P_H of 7.56 with sodium carbonate. These globulin solutions were tested with colloidal gold and the interesting observation was made that each globulin, regardless of its source, gave a typical paretic zone reaction. And also, the Wassermann reaction remained positive in the globulins prepared from syphilitic fluids, while negative globulins continued to produce negative Wassermann reactions. This bears out the statement of Weston that the gold precipitating substance is not the Wassermann reacting substance. Felton found that albumin protected the gold from precipitation by globulin and in this way he explained the zonal reactions produced by different fluids. Weston, in some unpublished experiments, dialyzed paretic fluids in parchment thimbles, which were impervious to albumin, against distilled water. Both the water and spinal fluid were covered with a layer of toluol but it was found that while the toluol did not interfere with the gold reaction, enough of it was absorbed by the fluid to cause hemolysis of the corpuscles used in the Wassermann reaction. He then dialyzed the fluids under aseptic conditions. A Wassermann and gold reaction were done on the fluid before it was placed in the thimble and the smallest amount of fluid which would cause complete inhibition of hemolysis in the Wassermann reaction was determined. In twelve hours fluid from the thimble and some of the same fluid from a test tube kept immersed in a jar of water placed on the table alongside the dialyzing tube, were tested for the gold and Wassermann reactions. It was found that the Wassermann dose for each fluid was the same, but that the gold curve from the thimble fluid did not give a greater reaction than 4. Twenty-four hours later the experiment was repeated and the gold reaction with fluid from the thimble was not greater than 1. The dose for the Wassermann reaction remained the same as that of the fresh fluid. The water in which dialysis had taken place was evaporated by a current of air from an electric fan to a quantity equal to that of the fluid taken for dialysis. The Wassermann was absolutely negative with this fluid but the gold reaction was the same as with fresh fluid except that there was one less 5 in the series. This loss of one 5 could be easily accounted for by loss in evaporating a large amount of fluid in a shallow dish. From the above data, it follows that the gold precipitating substance and the Wassermann reacting substance are different and can be separated from each other quantitatively. It also explains why one may have a reaction in the paretic zone with a spinal fluid which gives either a positive or negative Wassermann reaction.

RELATION OF THE GOLD REACTION TO THE WASSERMANN REACTION

Strangely enough the combination of a positive Wassermann and negative gold reaction in the spinal fluid does not occur with frequency. Felton mentions two fluids, 28F and 29Q, each of which gave a positive Wassermann but a negative colloidal gold reaction. No precipitate could be obtained by dialyzing these two fluids in collodion sacs. Others have reported instances of Wassermann positive fluids which gave negative gold reactions. Miller, et al, state that they never witnessed the combination of positive spinal fluid Wassermann reaction in association with a negative or weak colloidal gold reaction. In Table IV, page 401, of the same paper, they record case 16, ward M, as having a four-plus Wassermann reaction with each of three antigens and a gold reaction of 1221000000. It is generally conceded that such a curve could hardly be called luetic since many normal fluids have shown the same and even a greater number of 2's. In the paper of Miller and Levy, in cases C19, M81 and W118, a negative gold reaction is recorded with positive Wassermann reaction though the latter was positive to only one (cholesterolized heart) of three antigens. Case J155 showed a positive Wassermann with a negative gold reaction. Swalm and Mann in cases 63, 65, and 83; Farnell[21] in cases 10C and 17D; Potter in cases 24, 102, 12 and 28; Hammes[22] in cases 160, 175 and 92; Black, et al, in one case and Hulbert in case 2698 report positive Wassermann reactions in the fluid but negative gold reactions. Other observers have reported similar cases.

The instances in which paretic or luetic curves have been obtained with spinal fluids which showed a negative Wassermann reaction are fairly numerous. Usually in these cases, a history of infection or sufficient clinical evidence is present to at least strongly suggest a diagnosis of syphilis. Occasionally, however, paretic curves are obtained in cases where there is no history or clinical evidence of syphilis. Weston[23] reviewed 1500 routine examinations of the spinal fluid and found three instances in which the only positive reaction in the blood and fluid was a paretic gold curve in the latter. Fluid from these three patients was examined at intervals over the course of two and three years. One fluid showed an increase of globulin on two occasions, 24 and 36 cells, negative Wassermann reaction and a paretic gold curve on each of four occasions. On the fifth examination, made one year and eight months after the first one, a positive Wassermann reaction was obtained with the fluid. The second patient's fluid showed three reactions in the paretic zone and two negative ones. The blood and fluid Wassermann reactions were always negative. Fluid from the third patient showed similar reactions, i. e., three paretic curves and two negative ones with all other reactions negative. One c.c. of fluid was used in each Wassermann reaction. Comprehensive abstracts of the case histories were given and the question raised whether the paretic gold curve is ever persistently found in nonsyphilitics.

Felton's work shows that the paretic curve is due to globulin and that the other curves are due to varying proportions of globulin and albumin in the spinal fluid. He concludes that Lange's colloidal gold test is not specific for syphilis but is an accurate means of measuring the globulin present in the spinal fluid and indirectly the amount of albumin. It should be kept in mind that Felton's work must be viewed from the physicochemical standpoint and not from the point of view of the clinician. His conclusion is correct but the value of the test in neurosyphilis is not detracted from. It is quite evident from the recorded examinations of spinal fluids that the results of the gold test are quite constant in paresis, a trifle less so in tabes and cerebrospinal syphilis and negative in normal fluids. The occurrence of the paretic curve in clinically and serologically negative cases merely proves the presence of globulin in excess of albumin and does not prove the presence of syphilis. It does, however, suggest that the patient be observed over a long period of time and that repeated examinations of the spinal fluid be made. This is well illustrated in case 9037 in Weston's paper.

THE CELL COUNT, GLOBULIN TEST AND GOLD REACTION

Globulin determinations and cell counts are considered a necessary part of a routine examination of the spinal fluid. Unless there is an increase in the number of cells, the cell count is of no value. Mitchell, Darling and Newcomb[24] have shown that the cell count varies greatly in paresis and bears no relation to the mental or physical condition of the patient and the author has found that the cell count bears no relation to the gold reaction.

Globulin tests when taken alone are of little value. Increase of globulin has repeatedly been found in spinal fluid from nonsyphilitic patients suffering from various psychoses. The degree of parallelism between the globulin reaction and the paretic and luetic gold curves is fairly well marked.

The question of parallelism between clinical symptoms and the gold reaction might almost be dismissed with the remark that there is no parallelism between the two. In luetics, personal histories are notoriously unreliable and in many cases no clinical evidence of involvement of the central nervous system is found. Frequently, where routine Wassermann reactions on all patients are done, unexpected positives are obtained. Spinal fluids from such patients often show all the reactions positive and a gold reaction in the paretic zone. Southard and Solomon[25] have given the name *paresis sine paresi* to these cases. This type of case is not rare. Another type, and one not uncommon, is the treated patient who five or ten years after cessation of the treatment shows all the reactions in the blood and spinal fluid negative except the gold curve which is typically paretic. Between these two clinically negative but laboratory positive types and the outspoken paretic is a series of cases with gradually increasing clinical evidence of neurosyphilis. Nevertheless a paretic gold curve and often a positive Wassermann reaction will be obtained with the spinal fluid of these cases so that one is justified in concluding that there is no parallelism between the clinical evidence of neurosyphilis and the colloidal gold reaction. The latter may be and often is positive when the former is entirely absent.

SUMMARY

Methods for making colloidal gold and directions for doing the test are given. The characteristics of a good gold solution are stated and the nature of the substance causing the reaction is discussed. The combination of positive Wassermann reaction associated with a negative gold reaction is explained by the Wassermann reacting substance and the gold precipitating substance being two different and separable constituents of the spinal fluid. In paresis there is a parallelism between the Wassermann reaction and the gold curve. Fluid from clinically negative cases sometimes shows a typical paretic curve. Such findings call for minute clinical observation and repeated examination of the spinal fluid over a long period of time. There is not yet sufficient evidence to warrant the statement that such cases are syphilitic. Close observation, repeated examination of the spinal fluid and blood and microscopic examination of the brain and cord after autopsy in a great number of such cases is necessary before any justifiable conclusion can be reached. Chemically, the gold reaction is a test for the amount of globulin in spinal fluid and indirectly of the amount of albumin. Clinically, the test is of great value in that it furnishes corroborative evidence of neurosyphilis.

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THE COURSE TO TAKE IN THE PRESENCE OF DOUBTFUL CHANCRE

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THE presence of a doubtful chancre now involves one of the most difficult and embarrassing questions a physician is called upon to consider, and curiously enough this difficulty has arisen since attaining a precision in diagnosis unknown to our predecessors.

Formerly the course to be taken was laid down with exactitude. When the chancre was equivocal the physician should wait for the development of the secondary symptoms; the rash; the mucous patches, and the adenopathy. Nowadays this attitude has changed. The advantages of early treatment are so manifest, and the dangers of delay, with the fear of invasion of the central nervous system, are so great, that in doubtful cases, in which, nevertheless, there is a strong suspicion of treponemal infection, many thoughtful men advise beginning treatment on a provisional diagnosis. Every patient infected with the Treponema pallidum is now recognized as being potentially threatened with tabes or paresis, and the time between the localization of the virus and its dispersion is so short that delay exposes the physician to the reproach of being a ''hesitating practitioner,'' in a most critical situation. The saying has even become current that ''Every sore on the penis should be regarded as a chancre until proved otherwise.''

The question, however, is not quite so simple. The arguments against beginning treatment on suspicion, because of a trivial lesion, and almost all the lesions which may be mistaken for chancre are trivial, are that a man may be exposed not alone to a long, trying, and absolutely unnecessary medication, but also throughout his life may be tormented by the thought that he may have been infected. Furthermore, if the physician is in doubt as to the diagnosis, it is almost impossible to hide this doubt from the patient. This doubt on the part of the physician naturally reacts on the patient, and with a patient doubtful, it is difficult to carry out an effective, thorough, prolonged treatment. In other words, in order to attain effectiveness in treatment the patient must be in perfect accord with the physician, and the physician himself must have the moral support of certitude, for even if a patient, only presumably infected, starts out enthusiastically on a course of treatment, his enthusiasm, unless supported by facts, will gradually wane before the amount of treatment, which is now considered necessary, will be administered. This constitutes one of the greatest objections to a mere provisional diagnosis. The following case will illustrate some aspects of this important problem.

A highly neurotic patient, forty-one years of age, consulted me June 20, 1914, on account of a minute sore on the free surface of the glans penis near the corona, which had the red border, cup shape, and purulent base of herpes simplex. Later the peculiar significance of the position of this lesion will be discussed.

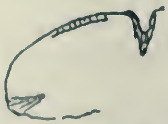
The patient said that he first noticed a little redness in this situation ten days before, and that he had been exposed venereally about three weeks previous to that. The patient was the very type, both digestively and nervously, to be subject to herpes. There was some soreness in the groins, with some soft swelling of the lymphatic nodules. A search was made for spirochetes, but none was found. The patient was, however, by no means satisfied, and consulted several men, all of whom returned the same negative answer, with a refusal to institute treatment. On July 6, the patient returned with what appeared to be an exacerbation or another attack of the same herpes of the glans, and at the same time he showed a herpes of the upper lip. The swelling of the lymphatic nodules in the left groin was now more marked.

On July 13 the blood was taken for a Wassermann test and was found positive. Two days later the blood was again taken and sent to two laboratories, one of which was the same as that in which the first test was made. The reports were strongly positive from one, and markedly positive from the other. The reactions, therefore, seemed to be greater for the second test than for the first, which would indicate an increasing dispersion of the virus.

The persistency of the lesion, the presence now of some not at all characteristic induration, the swelling of the lymphatic nodules in the left groin, which were also not characteristically indurated, and the presence of the positive serum reaction forced a diagnosis of syphilis, although no induration was present in the primary lesion, and a further search for spirochetes was fruitless.

It may be remarked here that the technical procedure of first swabbing the sore with alcohol, to induce a greater flow of serum, as advised by Klauder, might have been, if then known, of great advantage.*

It will be remembered that the patient first consulted me June 20, and that the sore then had been present ten days. The blood for the Wassermann was taken July 13, which was forty-three days after the appearance of the sore. The Wassermann reaction is usually not present till about twenty-five days after the appearance of the sore, and it therefore looks like neglect that Wassermann tests were not made frequently, at stated intervals, after the twenty-fifth day. I, however, saw the patient only twice in the interval between June 20 and July 13, once June 22, which probably was too soon, and once July 6, when undoubtedly the blood should have been taken. I was then so positive, however, that the affection was herpetic that I refused to believe in the possibility of syphilis, for besides having what appeared to be a herpes of the glans, he had a herpes of the upper lip. On July 13, however, the affection was felt to be continuing too long for a simple sore, and the Wassermann tests were made. A thorough treatment with arsphenamine and mercury was now instituted, which was followed by a rapid healing of the lesion, the sole symptom, together with the positive serum reaction and the swelling of the inguinal glands, the patient had ever shown. After this subsidence no further syphilitic symptoms have appeared, and the Wassermann reactions have since turned out constantly negative.



Schematic drawing to indicate the fan-shaped distribution of the arterioles in the sulcus and at the meatus, and the flat, horizontal distribution under the free surface of the glans.

At the sulcus and in the meatus there are also many glands; mucous glands at the meatus, and sebaceous glands in the sulcus, and each gland lies perpendicular to the free surface, and each is spun around by its own rete mirabile.

Involvement of these systems of arterioles would also give rise to deep perpendicular induration, and would therefore accentuate that of the fan-shaped distribution previously mentioned.

The absence of induration is one of the most embarrassing features in the diagnosis of a chancre. This absence is more frequent in some situations than in others, as, for example, on the upper aspect of the glans. In this situation it is slow in appearing, and when it does appear it may occur as a flat plate; "a visiting card induration,'' contrasting markedly with the deep split pea induration of a chancre in the sulcus, and the deep induration at the meatus. This difference has been ascribed to the difference in arrangement in the blood vessels; the main trunks of supply to the papillary layer of the mucous membrane running perpendicular to the surface in the sulcus and at the meatus, and parallel to the surface under the free surface of the glans. This accords with the well-known affinity of the Treponema pallidum for the heart and arteries.

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*Klauder, Joseph V.: The Early Diagnosis of Syphilis, Jour. Am. Med. Assn., March 8, 1919.

The sores which commonly, in this region, give rise to embarrassment in diagnosis are the soft sore (chancroid), pyogenic (streptococcic) infection, and herpes simplex.

Besides these there is the scabetic lesion, which at times so closely resembles chancre as to deserve the name the French give it of ''chancre scabetique.'' There are also the lesions of psoriasis and of lichen planus, which being scaly and inflammatory may give rise to a question of their being venereal.

When a sore exhibits the characteristics of chancroid, it should be treated with pure carbolic acid and iodoform, according to the technic prescribed by Scholz, which almost entirely eliminates the disagreeable odor, and secures a thorough adaptation of the medicaments to the diseased surface, and almost always is followed by prompt healing.

In streptococcic infection, treatment with warm boric acid applications, and boric acid salve should be employed. Calomel or oxide of mercury salves, commonly so effective in these infections, should be avoided because of their interference with the demonstration of the Treponema pallidum, and the consequent clouding of the early diagnosis of syphilis.

Atypical sores of the penis will always be the cause of worry, and the question is of such importance that it should always be kept before the profession with articles like that of Klauder's, in which the different types of chancre are well set forth. This is possibly the best means of keeping this question a live issue, and preventing it degenerating into formalism, as it did when we adopted the ritual of waiting for the secondaries, and as it will again tend to do should we adopt any such phrase as ''Every sore on the penis should be considered a chancre until proved otherwise.'' Such phrases and such rules of action tend to harness free thought instead of inciting it.

THE FIGHT AGAINST VENEREAL DISEASE IN THE EXTRACANTONMENT ZONE ABOUT CAMP ZACHARY TAYLOR

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THE LESSON

THE United States entered the European war with the lesson in regard to venereal disease and the fighting man clearly before her. Gonorrhea and syphilis had been more disastrous to the forces of the great powers of Europe than had been the bullets, gases and shells of the enemy. Those governments had not taken the proper precautions to protect their men and they had paid dearly for their mistake. There are ample proofs for these assertions. The most skeptical may start with the references published by the American Social Hygiene Association under the caption "Shall Venereal Disease Menace the Nation?" and find ample authentic statistics to dispel his skepticism.

GOVERNMENT PREPARATION

To meet this menace the United States mobilized and co-ordinated its resources promptly and effectively. One object only was in view and that was to make the men fit to fight. The marvelous foresight and thoroughness with which the campaign was planned and carried into effect augurs well for future public health. Those who are not familiar with it may learn its details by studying Publication III of the American Social Hygiene Association. The methods of attack divided themselves into four classes: (A) social measures to diminish sexual temptations; (B) education of soldiers and civilians in regard to venereal diseases; (C) prophylactic measures against venereal diseases; (D) medical care. The results obtained from the application of these methods in the extracantonment zone about Camp Zachary Taylor are the subject of this report.

THE FIGHT

Steps Taken for the Suppression of Prostitution.—Before Camp Zachary Taylor was opened for the mobilization of the United States troops the Secretary of War requested the local authorities to abolish the red light district in the city of Louisville. A similar request was made to all municipalities in the vicinity of the different cantonments established throughout the United States.

Following this request the Mayor of Louisville issued the necessary orders which resulted in the closing of all known houses of prostitution and the Chief of Police has earnestly enforced this order up to the present time.

In the beginning of this new regime there was considerable difference of opinion, even among the best citizens, as to the advisability of this measure, it being claimed by many that the abolishment of known houses of prostitution would simply result in the scattering of their inmates throughout the better residential sections of the city where they would not be under any kind of police surveillance. Undoubtedly this did occur in the beginning and still continues to a certain extent, but it has been demonstrated that, with a police force instructed to enforce the closing ordinance, public prostitution can be greatly reduced and it would appear to be possible to entirely abolish it in this way, should the community so desire.

In connection with the efforts of the civil police—and what has perhaps been an effectual stimulus to their efforts—a squad of military police in the beginning was assigned for duty inside the city of Louisville. They are under the direction of the Officer in Charge of the Law Enforcement Division of the Commission on Training Camp Activities and their services under this officer's efficient direction have been almost invaluable as an aid in controlling venereal infections among the soldiers at Camp Taylor.

The duties of the military police in this connection are to apprehend any person found soliciting soldiers on the streets or elsewhere in the extracantonment zone, to investigate any resort of questionable character and to aid in placing in quarantine persons known or suspected of having venereal infections, who, because of their methods of loose living, are endangering the health of the soldiers.

Suppression of Liquor Traffic.—By executive order all saloons and road houses within five miles of Camp Taylor were closed at the time the camp was opened to the soldiers. This order was enforced by the local authorities through the county patrolman and city police and resulted in the closing of many road houses and questionable resorts in the outskirts of the city. It can hardly be doubted that this step, taken in connection with the order prohibiting the sale of alcoholic drinks to soldiers in uniform, has been of greater benefit in protecting the soldiers against venereal infections than any other one measure adopted, the soldier in his sober senses being amenable to reason in sexual matters, whereas the soldier intoxicated is not.

Recreations and Social Surroundings.—With the abolishment of the saloon as a place to which the soldier might go for social recreation as well as alcoholic stimulation, it, of course, became necessary to establish other places for the gratification of his social instincts where he might not be subject at the same time to the temptations of alcohol and lewd women. This want was met by the creation of soldiers' clubs both within and without the camp and by the extension of activities by such organizations as the Y. M. C. A., Y. M. H. A., Knights of Columbus, and various other church and social organizations. In addition the War Camp Community Service arranged for soldiers' dances which were open almost continuously under proper chaperonage, so that it may be truthfully said that the soldier in the army need not lack for social recreation. Perhaps the majority of them, since their enlistment, have been given an opportunity of seeing social life from a broader and better angle than ever before.

Education in Regard to Venereal Diseases.—From the beginning of the establishment of Camp Taylor, when efforts were first made for the control of venereal infections in the extracantonment zone, certain measures were undertaken locally for the education of the civilian population as to the danger and importance of these diseases. With the creation of a new Division of Venereal Diseases in the Surgeon General's office of the Public Health Service, impetus was added to the local effort and means were furnished for carrying on a more complete campaign of public education in these matters.

The measures undertaken for civilian education in the Camp Zachary Taylor Civil Sanitary District have been along the following lines:

1. Publication of public health items in the local newspapers.
2. Distribution of pamphlets and other literature.
3. Exhibition of placards in public places.
4. Addresses delivered on venereal diseases.
5. Exhibition of moving picture films.

Prophylaxis and Quarantine.—Upon the adoption of the model venereal disease ordinance as a health regulation of the Jefferson County Board of Health (appended), the county health officer, who is also an acting assistant surgeon in the Public Health Service, undertook to enforce this ordinance in Jefferson County, and it is due to his efforts and the close cooperation which has been maintained between the Public Health Service and the local officials that a considerable measure of success has attended this effort.

In the first place it was necessary to set aside a place of quarantine for venereally infected persons who, because of their methods of living, were known to be a menace to the public health. It was also necessary to establish the legality of this quarantine through proper court decisions. Finally the proper personnel and the machinery for carrying on quarantine had to be evolved.

In designating a site for the quarantine of venereally infected persons, it was at once found that no proper building or institution for this purpose could be secured within the county and, since it was impossible to erect such a building, it was necessary to hold these persons in different institutions scattered throughout the city. The following institutions were selected for this purpose: the County Jail, the City Workhouse, the Union Gospel Mission, the Home of the Good Shepherd.

The majority of persons who have been held in quarantine have been placed in the County Jail and this institution has thus been badly overcrowded and considerable criticism has been made of the jail as a place of quarantine for this reason and because of its being a penal institution. Recently steps have been taken toward securing and equipping a ward in the City Hospital in which white women who are infected with venereal diseases may be quarantined and given proper hospital care pending their cure and rehabilitation.

Shortly after quarantine measures were instituted in this extra-cantonment zone habeas corpus proceedings were started against the county jailer for the release of an infected person held in quarantine under the direction of the county health officer. This case was tried before a judge of the Jefferson Circuit Court, Common Pleas Branch, Third Division, on the twenty-ninth day of July with four associate judges sitting. The legality of the quarantine for a reasonable length of time was upheld. Since this first habeas corpus proceeding a number of similar attempts have been made by infected persons to secure their release through the courts, but in each instance this has been denied.

In carrying out quarantine procedures it became necessary for the county health officer to delegate the power of quarantine to certain deputies who were in attendance at the police court in order that persons, who were reasonably suspected of having venereal infections and were therefore known to be a menace to the public health, might not give bond and escape at the time of its payment or upon their release by the police judge. In order to meet this difficulty the officer in charge of the Law Enforcement Division of the Commission on Training Camp Activities and the police court matron have been authorized to serve notice of quarantine on persons who are tried in the police court and who are known to have been guilty of immoral conduct either with civilians or soldiers. It has been of the greatest importance in the eyes of the local courts that extreme care be employed by the quarantine officer in his placing of suspected persons in quarantine. Possibly the attitude of the courts has been influenced by the fact that the only available place of quarantine in the beginning was the County Jail, but, whatever the cause, it has resulted in a rule established for the quarantine in this district that no person is to be suspected of infection with the venereal diseases unless they are known to have been guilty of immoral conduct.

The most important measures adopted for the control of venereal infections in the Camp Zachary Taylor extracantonment zone, as shown by the results of something more than a year's employment, will probably be ranked as follows:

1. Regulation of the sale of alcohol to U. S. soldiers.
2. Suppression of prostitution and police surveillance in extracantonment zone.
3. Popularization of the free venereal clinic.
4. Campaign for the education of the general public in the importance of venereal disease.
5. Quarantine of venereally infected persons of loose characters.

Medical Care.—At the beginning careful consideration was given to the available means of supplying proper medical care of venereally infected persons.

The central location of the new City Hospital and the already established venereal clinic in its out-patient department, as well as the availability and cooperation of its staff and its associated laboratory facilities, made it the natural and logical choice for the beginning of this work. By combining city and county support with the support of the federal government and the American Red Cross and by developing methods designed to encourage voluntary attendance, such as minimizing publicity—venereal patients can not be distinguished from others—providing male and female Red Cross nurses, a social service follow-up system, establishing a night clinic, etc., this clinic was enlarged to a remarkable extent as shown by the following tabulated statistics:

1918	NEW CASES	TOTAL TREATMENTS	DOSES OF ARSPHENAMINE
January	201	634	
February	243	909	42
March	241	1129	80
April	227	1214	95
May	252	1256	98
June	325	1438	304
July	336	1620	297
August	254	1603	433
September	289	1813	421
October	214	2203	417
November	199	1821	288
December	316	1981	274
1919			
January	383	2423	389
February	412	2657	301
Totals	3892	22701	3439

Treatment was also established in the County Jail and the City Workhouse and later in the Union Gospel Mission and the Home of the Good Shepherd with similar results. The laboratory work has been concentrated in the City Hospital under the direction of the Department of Pathology of the Medical Department of the University of Louisville. The increase of this work is shown by the following table of Wassermanns and smear examinations:

1918	WASSERMANNS	GONOCOCCUS SMEARS
January	60	—
February	114	—
March	120	—
April	89	—
May	170	—
June	189	40
July	240	61
August	223	41
September	238	117
October	202	244
November	174	381
December	166	570
1919		
January	254	619
February	254	613
	2493	2686

THE RESULT

The results of these measures have been most gratifying. While it is difficult to show concretely just how much good has been done it is undoubtedly true that a very large number of patients have been rendered noninfectious, not only among those unfortunate beings whose loose morals have made them objects of pay, but also among a very large number of indigent, nonvicious people who otherwise could not have afforded to secure proper treatment. In this connection the authorities have made every effort to treat only those who would not or could not go to private physicians.

It has been surprising to many to find that fully 75 per cent of patients examined have been infected with Spirocheta pallida or gonococcus. Of course these have been among the lower strata of society, but it is in these very classes that the most good needs to be done.

RECONSTRUCTION AND THE DUTY OF CIVILIANS

The time is approaching shortly when the federal government and the American Red Cross must withdrawn from direct support and control of this work. The campaign, however, will not be abandoned. The Kahn-Chamberlin bill will help to maintain the efforts so well established, but funds from this resource must be supplemented by moral and financial support on the part of the state, county and city to care for the unfortunates and protect society in the state's largest city. The authorities of each of these civil organizations are alive to the awakened public sentiment as well as to the social and economic importance of venereal disease control. The campaign can be put upon a money-saving and health-conserving basis. Venereal disease is a public menace and should be treated as any other communicable disease. Such infections will sap the vitality of the nation. The determined effort so well begun as a war measure must be maintained as a peace measure. Health and happiness are as essential in peace as in war. Disease, as well as immorality, is shameful. The army and navy in the past bore bad reputations because their statistics were known. Civil life has been much worse, but this is just being discovered. Its discovery will lead to its cure.

Women in quarantine can be made partially self-supporting and more self-respecting in a proper home. Steps have already been taken toward provision of such a home. The loneliness which leads to dissipation must be met with healthful amusements and attractive places of congregation. The saloon and lewd dance hall must be succeeded by the neighborhood house and similar institutions.

The measures so well established under the stimulus of making the soldier "fit to fight" are not likely to retrograde now the war is over. The "red light district" is a thing of the past. It has gone with whiskey. Plans are already under consideration for carrying on these most important public health activities and it is safe to say that public-spirited citizens and political leaders, alive to an awakened public conscience and the aroused sentiment of the people at large, will never allow a return to the old, sordid, wicked and expensive conditions.

NO. 81. SERIES 1918

AN ORDINANCE TO PREVENT THE SPREAD OF VENEREAL DISEASES

BE IT ORDAINED BY THE GENERAL COUNCIL OF THE CITY OF LOUISVILLE:

Venereal Diseases Declared Dangerous to the Public Health: Syphilis, gonorrhea, and chancroid, hereinafter designated venereal diseases, are hereby declared to be contagious, infectious, communicable, and dangerous to the public health.

Section 1. *Venereal Diseases to be Reported.*—Any physician or other person who makes a diagnosis in, or treats, a case of syphilis, gonorrhea, or chancroid, and every superintendent or manager of a hospital, dispensary, or charitable or penal institution, in which there is a case of venereal disease, shall report such case immediately in writing to the Health Officer of the city of Louisville, stating the name and address or the office number, age, sex, color, and occupation, of the diseased person, and the date of onset of the disease, and the probable source of the infection, provided, that the name and address of the diseased person need not be stated except as hereinafter specifically required. The report shall be inclosed in a sealed envelope and sent to the Health Officer of the city of Louisville, who shall report at least once in every three months on the prescribed form to the State Board of Health, all cases reported to him.

Section 2. *Patients to be Given Information.*—It shall be the duty of every physician and of every other person who examines or treats a person having syphilis, gonorrhea, or chancroid, to instruct him in measures for preventing the spread of such disease, and inform him of the necessity for treatment until cured.

Section 3. *Investigation of Cases.*—The city health officer shall use every available means to ascertain the existence of, and to investigate, all cases of syphilis, gonorrhea, and chancroid within the city of Louisville, and to ascertain the sources of such infections. The health officer is hereby empowered and directed to make such examinations of persons reasonably suspected of having syphilis, gonorrhea, or chancroid, as may be necessary for carrying out these regulations. Owing to the prevalence of such diseases among prostitutes and persons associated with them, all such persons are to be considered within the above class.

Section 4. *Protection of Others from Infection by Venereally Diseased Persons.*—Upon receipt of a report of a case of venereal disease it shall be the duty of the health officer to institute measures for the protection of other persons from infection by such venereally diseased person.

(A) The health officer is authorized and directed to quarantine persons who have, or are reasonably suspected of having syphilis, gonorrhea, or chancroid whenever, in the opinion of said health officer, or the State Board of Health, or its secretary, quarantine is necessary for the protection of the public health. In establishing quarantine the health officer shall designate and define the limits of the area in which the person known to have, or reasonably suspected of having syphilis, gonorrhea, or chancroid and his immediate attendant are to be quarantined and no persons other than the attending physicians shall enter or leave the area of quarantine without the permission of the health officer.

Every breach of such quarantine and every refusal to abide by it shall be considered a violation of this ordinance and each hour such breach or refusal continues, shall be considered a separate violation.

No one but the health officer shall terminate said quarantine, and this shall not be done until the diseased person has become noninfectious, as determined by the local health officer or his authorized deputy through the clinical examination and all necessary laboratory tests, or until permission has been given him so to do by the State Board of Health or its secretary.

(B) The local health officer shall inform all persons who are about to be released from quarantine for venereal disease, in case they are not cured, what further treatment should be taken to complete their cure. Any person not cured before release from quarantine shall be required to sign the following statement after the blank spaces have been filled to the satisfaction of the health officer:

"I, ... residing at ...., hereby acknowledge the fact that I am at this time infected with ...., and agree to place myself under the medical care of .... with .... hours, and that I will remain under treatment of said physician or clinic until released by the health officer of the city of Louisville or until my case is transferred with the approval of said health officer to another regularly licensed physician or an approved clinic.

I hereby agree to report to the health officer within four days after beginning treatment as above agreed, and will bring with me a statement from the above physician or clinic of the medical treatment applied in my case, and thereafter will report as often as may be demanded of me by the health officer.

I agree, further, that I will take all precautions recommended by the health officer to prevent the spread of the above disease to other persons, and that I will not perform any act which would expose other persons to the above disease.

I agree, until finally released by the health officer, to notify him of any change of address and to obtain his consent before moving my abode outside his jurisdiction.

....
(Signature)

....
(Date)

All persons signing the above agreement shall observe its provisions, and any failure so to do shall be a violation of this ordinance. All such agreements shall be filed with the health officer and kept inaccessible to the public as provided in Rule 10."

Section 5. *Conditions Under which the Name of a Patient is Required to be Reported.*—(A) When a person applies to a physician, or other person for the diagnosis or treatment of syphilis, gonorrhea, or chancroid, it shall be the duty of the physician or person so consulted to inquire of and ascertain from the person seeking such diagnosis or treatment whether such person has theretofore consulted with or has been treated by any other physician or person last consulted. It shall be the duty of the applicant for diagnosis or treatment to furnish this information, and a refusal to do so or a falsification of the name and address of such physician or person consulted by such applicant shall be deemed a violation of this ordinance. It shall be the duty of the physician or other person whom the applicant consults to notify the physician or other person last consulted of the change of advisers. Should the physician or person previously consulted fail to receive such notice within 10 days after the last date upon which the patient was instructed by him to appear, it shall be the duty of such physician or person to report to the local health officer the name and address of such venereally diseased person.

(B) If an attending physician or other person knows or has good reason to suspect that a person having syphilis, gonorrhea, or chancroid is so conducting himself or herself as to expose other persons to infection, or is about so to conduct himself or herself, he shall notify the health officer of the name and address of the diseased person and the essential facts in the case.

Section 6. *Druggists Forbidden to Prescribe for Venereal Diseases.*—No druggist or other person not a physician licensed under the laws of the State shall prescribe or recommend to any person any drugs, medicines, or other substances to be used for the cure or alleviation of gonorrhea, syphilis, or chancroid, or shall compound any drugs or medicines for said purpose from any written formula or order not written for the person for whom the drugs or medicines are compounded and not signed by a physician licensed under the laws of the State.

Section 7. *Spread of Venereal Disease Unlawful.*—It shall be a violation of this ordinance for any infected person knowingly to expose another person to infection with any of the said venereal diseases or for any person to perform an act which exposes another person to infection with venereal disease.

Section 8. *Prostitution to be Repressed.*—Prostitution is hereby declared to be a prolific source of syphilis, gonorrhea, and chancroid, and the repression of prostitution is declared to be a public health measure. The health officer is therefore directed to co-operate with the proper officials whose duty it is to enforce laws directed against prostitution and otherwise to use every proper means for the repression of prostitution.

Section 9. *Giving Certificates of Freedom from Venereal Disease Prohibited.* Physicians, health officers, and all other persons are prohibited from issuing certificates of freedom from venereal disease, provided this rule shall not prevent the issuance of necessary statements of freedom from infectious diseases written in such form or given under such safeguards that their use in solicitation for sexual intercourse would be possible.

Section 10. *Records to be Secret.*—All information and reports concerning persons infected with venereal diseases shall be inaccessible to the public except in so far as publicity may attend the performance of the duties imposed by these regulations and by the laws of the State.

Section 11. The duties and authority herein imposed on and given the Health Officer may be performed and exercised by any of his assistants.

Section 12. Any person violating any of the provisions of this ordinance shall be fined not less than Five ($5.00) dollars nor more than Fifty ($50.00) dollars.

Section 13. This ordinance shall take effect from and after its passage.

THE TREATMENT OF SYPHILIS IN TUBERCULOUS PATIENTS

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IT has been recognized for years that syphilis and tuberculosis are frequently found in the same individual. The number of recognized cases, however, has grown tremendously with the advent of the Wassermann reaction. At the same time internists have become more alert in their search for clinical evidence of the dual infection. The literature is full of data as to the incidence of tuberculosis among syphilitics. Opinions, however, vary widely as to the percentage of cases showing both infections. Tedeschi[1] claims that 70 per cent of the cases of tuberculosis developing during a period of ten years in his prison service occurred on a luetic soil, while Letulle[2] reports 19 per cent of 346 tuberculous inmates of Bouchiecaut Hospital had positive Wassermanns. Bronfenbrenner[3] examined 193 syphilitics for tuberculosis with Besredka's tuberculous antigen and found that 83 cases, or 43 per cent, were positive. Fifty-five of these were clinically tuberculous, while 28 were not diagnosed. In order to make a comparison with these figures he then examined 432 nonsyphilitics and found 100 cases, or 23.15 per cent, tuberculous. Thus, he concludes that tuberculosis is much more frequent among syphilitics than in nonsyphilitics. This he attributes to the syphilis as such, or to antisyphilitic treatment markedly lowering the resistance of the patients so as to make them more susceptible to a new infection of tuberculosis, or rendering them less resistant against the progress of the disease previously contracted. The foregoing percentages are somewhat higher than those of the average hospital. Lyons[4] examined 471 cases of tuberculosis and found that 6 per cent of these gave a positive Wassermann reaction. He does not state, however, how many of the negative cases showed evidence of syphilis upon examination. In the University Hospital we have found about 3 to 5 per cent of our syphilitics have shown evidence of Koch infection. This low percentage may be explained by the fact that a very large portion of our cases of syphilis are seen in the primary or early secondary stages of the disease. We have found tuberculosis to be more commonly associated with the older syphilitic lesions.

Before the advent of salvarsan, mercury was the drug *par excellence* in the treatment of syphilis. Due to the fact that patients with both syphilis and tuberculosis showed improvement under mercurial treatment, a number of clinicians became overenthusiastic about the use of this drug in the treatment of tuberculosis. Even as recently as 1908 Wright[5] reports a series of 65 supposedly uncomplicated cases of tuberculosis treated with succinimide of mercury injections, all of whom showed improvement. He also had 41 controls under the same hygienic treatment who did not receive mercury. The condition of these remained stationary. Previous to the institution of this form of therapy his death rate had been 11.29 per cent, which was reduced to 4.76 per cent following the administration of the drug. Thus he concludes, after observing these patients for a few months, that mercury offers great hope as a therapeutic agent in the treatment of tuberculosis. In order to further test the therapeutic effect of mercury Hartz[6] selected 14 cases of active tuberculosis to whom he gave mercurial injections. Within one year 12 of these cases, or 85.7 per cent, died, while the other two had pulmonary hemorrhage. He states that for a time some of them showed a temporary improvement. This he could not definitely attribute to the mercury, but rather to the hygienic treatment. Eventually all patients began to deteriorate almost in direct proportion to the amount of mercury received. Many other observers have had similar experience and it is now generally conceded that mercury should be given with great care to the tuberculous individual.

Finally, realizing the dangers produced by mercury in the treatment of the dual infection, clinicians hailed the advent of salvarsan with great enthusiasm and many optimistic results have been recorded from its use. I wish to present the data on a few cases treated with arsphenamine in the University Hospital.

CASE REPORTS

CASE 1.—Male, age twenty-five. Examination revealed a maculopapular rash over the body with an involuting primary sore on the genitals. There was a general adenopathy and the spleen was felt 2 fb. below the costal margin. Wassermann positive. Tuberculosis was not suspected. On entrance the patient was given 0.3 grams of arsenobenzol intravenously, following which he suffered no reaction, the temperature remaining normal each day for the following week. One week following his first injection, he received 0.4 grams of diarsenol intravenously. Eight hours after the injection his temperature reached 102° with accompanying subjective symptoms. Two hours later the temperature had risen to 103.2°. It gradually fell to 99° the following morning. It again arose in the afternoon to 102°. The patient was kept in bed and within ten days the afternoon temperature gradually became normal. He was referred to the Department of Internal Medicine, which reported tuberculosis of the left apex as evidenced by definite dullness, crackling rales, prolonged expiration and slight bronchial breathing. X-ray examination showed slight cloudiness in this region.

Case 2.—Female, age sixty-three. Typical gummatous ulcers of the left arm, one of which involved the radius, and gummatous periostitis of the right tibia. Wassermann four-plus. Suspected tuberculosis. The patient was given 0.2 grams of neosalvarsan intravenously, following which she suffered no reaction. One week later the patient received 0.25 grams neosalvarsan intravenously. In a few hours she felt slightly indisposed with headache and a slight rise in temperature. She continued to run a temperature from 99° to 100° on each afternoon for four or five days, in spite of the fact that she was kept constantly in bed. At another weekly interval she was given a third dose of 0.25 grams neosalvarsan intravenously. Within six or eight hours her temperature reached 101.8°. She began to cough and raise a considerable amount of sputum. Examination of this sputum for tubercle bacilli was negative. The gummatous lesions showed marked evidence of involution. However, her afternoon temperature for the following week remained between 100° and 101°. At another weekly interval the patient received her fourth intravenous injection of 0.3 grams of neosalvarsan following which she had the usual reaction. She was referred to the Department of Internal Medicine, who reported tuberculosis of the left lung. X-ray examination showed an old tuberculous process of the left apex externally to the medial portion of the lung. Five weeks after the patient's entrance into the hospital she was discharged, the gummatous lesions having entirely healed. However, she was still running an afternoon temperature, and was losing gradually in weight and strength.

Case 3.—Male, age thirty. Diagnosis: lues hereditaria. Examination showed an old interstitial keratitis, slight bony changes and total deafness. Wassermann four-plus. Lungs not examined. During the course of a month the patient received four injections of arsenobenzol, the initial dose being 0.3 grams, gradually increasing to 0.5 grams. During his stay in the hospital he showed no evidence of temperature or other symptoms that would lead one to suspect pulmonary involvement. He was discharged with instructions to take mercurial inunctions. The patient entered the clinic of Internal Medicine about a year later on account of pulmonary hemorrhage. Physical examination showed a marked involvement of the left lung. X-ray report: Unilateral involvement in an old tuberculosis process. Entire upper left lobe is almost uniformly dense. The lower margin of the lobe is sharply outlined while all structures are lost in the upper portion. The middle lobe shows relatively few lesions anteriorly and centrally. Diagnosis, old tuberculosis, fibroid type. The patient remained in the hospital only a few days and the details of his death a few weeks later could not be obtained.

Case 4.—Male, age forty. Diagnosis: lues latens. Tuberculosis involving the uvula and posterior pharynx. Suspected tuberculosis of the lungs. The patient was given 0.3 grams of arsenobenzol, following which he developed a temperature of 101.6°. At his request he was discharged from the hospital the following day to return in one week, at which time his temperature varied between 100° and 103°. In the meantime he had developed a severe cough, felt very bad, and had lost slightly in weight. X-ray report: An old process of both apices with a recent process extending uniformly throughout the chest. Diagnosis, pulmonary tuberculosis. Grave prognosis.

Case 5.—Male, age forty-two. Presented a gummatous lesion involving the soft palate. Wassermann four-plus. Medical diagnosis: tuberculosis of the left apex, confirmed by x-ray examination. The patient received 0.2 grams neosalvarsan, following which he suffered no reaction and stated that he felt better, having gained slightly in weight. One week later he received 0.3 grams neosalvarsan intravenously, following which he developed a slight cough. Due to this fact the interval between his injections was lengthened from one to two weeks, the patient receiving in all six injections. The cough increased in severity and the patient developed rather marked pleuritic pains, and when he was discharged was running a slight afternoon temperature.

Case 6.—Female, age thirty-one. Examination showed an extensive follicular secondary syphilitic eruption, and a marked moth-eaten alopecia. Wassermann four-plus on both blood and spinal fluid. Suspected tuberculosis. The patient was examined three months previous to her entrance by an internist, who reported slight involvement of the left lung. She received 0.3 grams arsenobenzol. Twenty-four hours later her temperature was 101.4°. One week later she received 0.4 grams arsenobenzol intravenously, with a rise of temperature to 99.2°. The following week she received a third injection of .5 grams arsenobenzol with a slight rise in temperature. Following her fourth injection of .05 grams arsenobenzol she developed a pain in the chest which gradually increased in severity. Physical examination at this time showed an increase in the physical signs over both apices with distinct dullness at the left base. X-ray report: Tuberculosis of both apices principally of fibroid type. Changes at left base apparently due to an acute intercurrent disease.

Case 7.—Male, age twenty-seven. Maculopapular eruption with a definite primary syphilitic lesion. General adenopathy. Wassermann four-plus. The patient received 0.3 grams old salvarsan. Within a few hours the temperature reached 104°. This, however, gradually fell to normal the following day. One week later he received a second intravenous injection of 0.3 grams old salvarsan, following which he suffered no reaction. At his next weekly interval the patient received an intravenous injection of 0.4 grams old salvarsan, following which he developed a temperature of 103.3°, with accompanying subjective symptoms. On the next day his afternoon temperature reached 104°. The third afternoon it was 102.8°. The fourth afternoon it was 101.6°, and gradually fell to normal. Physical examination showed rather marked changes in the left apex. X-ray examination was not made and the patient disappeared from the clinic.

Case 8.—Male, age thirty. Tuberculosis of the right knee of ten years standing. Wassermann four-plus. The patient was having only slight symptoms from the knee condition. He was given 0.3 grams of arsenobenzol intravenously.

Within a few hours the knee began to swell, became red and extremely painful. At the same time the patient's temperature was elevated. Although the patient was not in the habit of taking opiates, he required a grain of morphine before any relief from the pain was obtained. He was sent to the Department of Orthopedics, where a plaster cast was placed on the leg. When the patient was visited the following morning it was found that he had removed the cast during the night by means of an iron bar on account of the excruciating pain. After suffering for ten days he entered the City Hospital in St. Louis and had the leg amputated.

CASE 9.—Young girl, age sixteen. Diagnosis: lupus vulgaris of the chin and left hand dating since infancy. She was given 0.3 grams arsphenamine intravenously. Within two hours the lesions became swollen, of a bright red color, but not associated with subjective symptoms. This hyperemia with some edema reached its height in about 8 hours and gradually began to fade. The following day no evidence of the reaction remained.

CASE 10.—Female, age thirty-five. Medical diagnosis: pulmonary tuberculosis. No tubercle bacilli found on repeated careful examination of sputum. Five years later the patient presented herself complaining of ''tuberculosis of the skin.'' Examination revealed a diffuse nodular syphilide of the left shoulder and back, and right upper and forearm, also of the forehead. Marked leucoplakia of the tongue. Marked general adenitis. Tactile fremitus was elicited over the right front and back, most marked over the lower lobe, with signs of consolidation, many rales and tubular breathing. Under three injections of neosalvarsan the entire skin eruption disappeared. Simultaneously the lung signs and symptoms cleared up completely and the patient gained materially in weight. Today, four years later, she is in perfect health. Diagnosis: Syphilis of the lungs.

CASE 11.—Boy, age fifteen. Diagnosis; lues hereditaria. Markedly stigmatized with active syphilitic arthritis of left elbow and wrist, and right wrist; also pain in left heel and nocturnal pain in right foot. Medical diagnosis: pulmonary tuberculosis. Sputum negative for tubercle bacilli upon repeated careful examination. No focal reaction or rise in temperature resulted from subcutaneous injection of 8 milligrams of tuberculin. X-ray showed involvement of the left apex, with cavity in the left lower lobe. The patient received four weekly injections of neosalvarsan, the first being 0.2 grams intravenously, and subsequent injections being 0.3 grams. The patient's condition improved rapidly and he gained in weight. One year later the patient returned to the hospital perfectly well and having undergone considerable physical development. His treatment during the interval had consisted of mercurial inunctions. Diagnosis: pulmonary syphilis.

CASE 12.—Male, age twenty-seven. Examination showed emaciation, cachexia, weakness and cough. Retraction of chest above left clavicle. Necrosis of small bones of nose. Perforation of septum. Necrotic sinus extended from buccal cavity at site of canine fossa through the left antrum of Highmore and into the left nares. Wassermann positive on both blood and spinal fluid. Tactile fremitus was increased over the right front and back. Change in whispered voice over the third and fourth ribs in front. Definite impairment and marked cracked-pot resonance. Tubular breathing and moist rales. Prolonged expiration over both apices. Bases clear. X-ray report: Definite involvement of the left apex as low as the second rib, marked by stippling and a general haziness. Right apex relatively clear. Hilus shadows exaggerated on both sides. The patient received an intravenous injection of 0.2 grams old salvarsan from which he suffered no reaction. Following this first treatment the general condition became immediately improved, the cough became less frequent and less productive, and the night sweats were less severe. One week later he received a second intravenous injection of 0.4 grams old salvarsan from which he suffered no reaction. He had already gained considerably in weight. The night sweats had ceased. Subsequently he was given four weekly intravenous injections of 0.6 grams old salvarsan with continued improvement. He was discharged from the hospital, the tertiary process involving the maxilla having healed, leaving a permanent sinus. The signs of cavity in the right lung were diminished. Four months later the patient returned for observation. He weighed more than ever before. The night sweats had disappeared. He had no cough and felt perfectly well. Diagnosis: syphilis of the lung.

Cases 1, 4, 6, 7, and 8 showed a rise in temperature following the first injection. In case 7, however, the reaction was more of the type of a toxic reaction such as is caused by the use of impure water in the salvarsan solution. In this case the temperature came down to normal within a few hours and remained normal until his third treatment, when he developed the typical temperature curve of a tuberculous patient.

Cases 1 and 8 showed rather violent reactions within a very short time after their injections.

Cases 8 and 9 (tuberculosis of the joint and lupus vulgaris) showed marked focal reactions which were similar in all respects to that which may be elicited by the injection of tuberculin.

Case 3 was unusual in that the patient showed no reaction whatever during his course of arsenobenzol, but returned a year later with pulmonary hemorrhages and died within a very short time. This apparently delayed exacerbation may be partially accounted for by the ignorance of the patient and the fact that he was totally deaf and a definite history of what had transpired during the past year could not be obtained.

Cases 2, 5, and 6 showed very much milder reactions than the previous cases; due to the fact that tuberculosis was suspected, the patients were given smaller doses, and in Case 5, the treatments were administered at greater intervals of time. This brings up the point of dosage and intervals which should elapse between treatments where there is an obvious tuberculosis present in the syphilitic. Fordyce[7] states that small doses of salvarsan seem to have a tonic effect on tuberculosis and he advises 0.2 grams to 0.25 grams with an interval of two to four weeks, depending upon the severity of the infection.

Cases 10, 11 and 12 were diagnosed syphilis of the lung and all responded beautifully to specific treatment.

The above findings are not exactly in accord with those of all observers. In an analysis of 375 cases treated, Sieskind[8] states that he treated patients with hemoptysis and with phthisis in various stages without ill effect, and always with general improvement and an increase in weight. Klowklow[9] states that in the treatment of 12 tuberculous patients with salvarsan the pulmonary lesions of three showed improvement, while two lost their bacilli. Although some of the patients had a slight rise in temperature following their injections, he states that in the twelve cases thus treated, he could detect no ill effects which could be attributed to the salvarsan.

Hartley,[10] after treating 16 tuberculous patients with salvarsan, states that the pyrexia which had resisted all previous measures, responded beautifully to the drug. He cites four cases with charts in favor of the antipyretic power of salvarsan. Foguioli,[11] Bernard and Paraf,[12] Jaquet,[13] and others have also reported favorable results. Herxheimer and Altmann,[14] on the other hand, have reported a series of cases which so nearly correspond to my own that I give a brief review of them.

CASE 1.—Patient with a macular eruption over the body and lesions on the tonsil. Wassermann positive. One year previously the patient had a tuberculous gland on the left side of the neck removed surgically. This resulted in healing. Some months later a small hard, painless swelling appeared in this locality. The patient received 0.5 grams arsenobenzol intramuscularly. The following day he suffered a Herxheimer reaction. Two days later there was pain at the site of the swelling which soon became soft and showed slight fluctuation. On incision a caseous pus was obtained. A portion of this was injected into animals and the tubercle bacillus was recovered.

CASE 2.—Diagnosis: multiple cutaneous gummata. Ten years previously patient had pleuritis. Under two years of hygienic treatment this disappeared and the patient remained in good health. Lung examination negative. He received 0.5 grams arsenobenzol intramuscularly. Fourteen days later the gummous lesions had healed and the patient was discharged. He returned in four weeks with a recurrence and received .6 grams arsenobenzol intramuscularly. The lesions healed slowly. Three weeks after the second injection he developed a sudden temperature of 38.2° C. with headaches, severe cough, and pain in chest.

CASE 3.—Diagnosis: syphilis. No history of lung trouble was obtainable. Physical examination negative. The patient received 0.4 grams salvarsan intravenously. He returned in three weeks complaining of general weakness and showed marked emaciation. Physical examination showed dullness and increased rales at the left apex. X-ray examination showed a slight cloudiness of this area.

Case 4.—Physical examination of the lungs negative. The patient received 0.5 grams arsenobenzol intravenously. Five days later he developed a slight cough with sputum. On examination numerous fine moist rales were heard at both apices. Eleven days later the patient died as a result of a thrombus. Autopsy revealed encapsulated caseous masses in both apices and adhesions in the pleura.

In summing up these cases, Herxheimer and Altmann state that they all presented the same reaction; that is, the latent tuberculosis flared up while the luetic lesions healed under salvarsan therapy.

As a further test, they picked out four cases of lupus vulgaris to which they administered small doses of salvarsan. In each instance, within a very short time after the injection, they noticed a focal reaction which reached its height within four to six hours and gradually subsided.

Thus it is seen that Herxheimer and Altmann's cases reacted in every instance in the same manner as those which I report. Wechelmann[15] has collected from the literature ten deaths occurring in patients with syphilis and tuberculosis treated with salvarsan, which he attributes to the treatment. Courmont and Durand,[16] administered arsenobenzol (Billion) to two patients, one a tabetic with fibroid caseous tuberculosis, in whom the treatment seemed to aggravate the pulmonary condition and diminish his weight. The second, who gave a history of numerous attacks of pleurisy, and who showed a consolidation at one apex, was much benefited. On numerous occasions examination failed to reveal tubercle bacilli. Culver,[17] has recently described a case which on physical examination presented all the evidence of a clinical tuberculosis, without tubercle bacilli. This case responded within a very short time to neosalvarsan and mixed treatment. Thus, he justly concludes that this was most likely a case of pulmonary syphilis.

It seems very probable that many of the cases supposedly tuberculosis of the lung, who have responded to large doses of salvarsan, have been syphilis rather than tuberculosis. It is by no means an easy task to differentiate between syphilis and tuberculosis of the lung, as is evidenced by the symptoms and physical findings in 119 cases of undoubted syphilis of the lung collected from the literature by Wile and Karshner.[18] The symptoms in 103 cases were as follows:

98 cases had cough; 78 cases raised sputum; 39 cases had dyspnea; 9 had hoarseness; 8 had chills; 51 had fever; 36 had night sweats; 42 had pain in the chest. There is hemoptysis in 42 cases. The physical findings were stated in 98 cases as follows: both lungs involved in 33; right apex 42; right middle lobe 18; right base 20; left apex 45; left base 28; 18 cases showed lessened movement, or retraction; 53 cases showed impairment; 61 cases showed rales; 27 showed cavity. Breath sounds were increased in 16 cases; diminished in 16. There was tubular breathing mentioned in 21. Two showed pneumothorax. One showed pyopneumothorax. One had empyema. Seven cases had pleural effusion. There was friction in 3 cases.

Thus it is seen that both the symptoms and physical findings in these cases of pulmonary syphilis are parallel to the symptoms and findings in tuberculosis of the lungs.

CONCLUSIONS

From the foregoing considerations, one can justly conclude that mercury should be used with great care in tuberculous patients, that the deleterious effect is not immediate, but appears several months after the institution of administration of the drug, as was pointed out by Hartz.[6] Therefore, arsphenamine (salvarsan) seems to be the drug of choice in such cases, but should be given in small doses at long intervals, inasmuch as the ordinary dosage accentuates active foci and is prone to cause a flare up in latent lesions.

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[18] Wile and Karshner: Not published.

Abstract of Current Syphilis Literature

It is the purpose of this Journal to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs, Arkansas.

WM. H. DEADERICK, M.D., EDITOR

A VARIETY OF MASSIVE SYPHILITIC SPLENOMEGALY ATTENDED BY REMARKABLE VASCULAR CHANGES.—Douglass Symmers, New York. Surgery, Gynecology and Obstetrics, 1919, vol. xxviii, p. 58.

There is a distinctive form of massive splenomegaly marked by the occurrence in the splenic substance of variable numbers of pinhead-sized, rounded, oval, or angulated bodies with a brownish or yellowish brown, granular looking center, and with or without a peripheral zone of red cells. These bodies, which correspond, histologically, to sclerosis and mineralization of the smaller arteries, are characteristic and readily identified, and are distinct from anything familiarly encountered in the naked eye examination of the spleen. The substance of the spleen presents a reddish, flesh-like appearance, is leathery in consistence, and shows, on section, numerous small vessels whose walls are pale and thickened, corresponding, microscopically, to venules in or around which hyaline deposits have occurred, but which are immune from infiltration by mineral salts. Hemorrhages may be seen by the naked eye and, histologically, are found in various stages of organization. In addition, the splenic substance is extensively replaced by the productive overgrowth of connective tissue of inflammatory origin. The variety of splenomegaly described was encountered in syphilitic subjects only. The selective mineralization of the small arteries, while differing from the changes commonly found in syphilitic vessels, appears nevertheless to represent the deposition of salts in tissues already injured by syphilis. Whether identical changes occur in vessels in association with diseases other than syphilis, remains to be seen.

A REPORT OF THE PATHOLOGICAL CHANGES OF THE BRAIN IN 162 CASES OF PARESIS.—Thomas B. Christian, Norristown, Pa. American Journal of the Medical Sciences, 1919, vol. clvii, p. 271.

The pathologic findings in 162 cases of paresis and the percentage of each finding are summarized as follows: chronic leptomeningitis 100 per cent, chronic pachymeningitis 81, hydrops meningeus 72, cranial ependymal sclerosis 71, dilated cerebral lateral ventricles 60, cerebral cortical atrophy 54, cerebral arteriosclerosis 43, cranial osteosclerosis 42, cystic chorioid plexuses 33, chronic internal hemorrhagic pachymeningitis 17, pachycephalitis 14, cerebral softening and edema 14, cerebral congestion 10, chronic external and internal adhesive leptomeningitis 8, dilated fourth ventricle 5, coherent cerebral hemispheres 4, softening of velum interpositum 3, small thrombotic lenticular softenings 3, cerebral edema and softening 2, cystic and cheesy degeneration of chorioid plexuses 2, general cerebral atrophy and sclerosis 2, thrombotic softening of lenticular nucleus close to the posterior limb of the internal capsule 2, old area of thrombotic softening of both caudate nuclei 2. Findings appearing only once in the series are as follows: congested and thickened velum interpositum and softened pituitary body, chronic adhesive pericranitis, dilated third ventricle, cerebral hemorrhage, dilated cerebral perivascular lymph space, cerebellar tumor, thrombotic softening of right caudate nucleus and part of anterior and posterior limbs of the internal capsule, calcification of falx cerebri, small perivascular cerebral and cerebellar softenings, tuberculoma of dura, old hemorrhage of the right caudate nucleus, thrombotic softening of the left putamen of the lenticular nucleus, thrombosis of the right anastomotic vein of Trolaid, cyst of the pia and arachnoid, softening of the left cerebellar hemisphere involving the lobus semilunaris, lobus posteroinferior, lobus quadrangularis from thrombosis of the left vertebral and of the left posteroinferior cerebral arteries, thrombotic softening of the posterior limb of the right internal capsule, calcified nodules of the left temporal pole, spindle-celled sarcoma of the right optic thalamus, absence of middle commissure of optic thalamus, small thrombotic cortical softenings of left cerebellum and right occipital lobes, anomalous anterior cerebral arteries, thrombosis of the right lateral and superior longitudinal sinus, thrombotic softening of the right lenticular nucleus and double optic atrophy, thrombotic softening of the left cerebellar white tracts. The microscopic findings were practically similar in the cases examined and consist of the following in general: syphilitic perivascular round and plasma cell exudate, distortion of cerebral cortical layers, chronic ganglia cell degenerative changes and cerebral gliosis, acute and chronic degenerative ganglia cell changes with atrophy, endarteritis and pericarditis.

SYPHILIS AS A CAUSE OF BACKACHE.—Percy Willard Roberts, New York City. New York State Journal of Medicine, 1919, vol. xix, p. 20.

The cases of back pain which have been observed in this study fall under the general classification of myositis. Their symptomatology suggests irritation of muscle and fibrous tissue by some toxic material, and the degree of discomfort ranges from dull lumbar backache to acute pain on any attempt at motion. Except for tenderness on deep pressure in the gluteal and lumbar regions no characteristic features have marked these cases, and the diagnostic perplexities they presented may be judged by the fact that they had been treated for a variety of disorders including uterine displacements, sacroiliac strain, Pott's disease, scoliosis and floating kidney, and in one woman a diagnosis of carcinomatosis was ventured. While it has not always been possible to demonstrate the presence of syphilis in these patients, the fact remains that they all presented certain evidence of an hereditary taint and that the symptoms cleared up under mixed treatment. Throughout this study of orthopedic conditions due to inherited syphilis a clue to diagnosis has been found in the teeth. It is not to be assumed that any dental anomaly is conclusive evidence that the patient has syphilis. Proof is still lacking that these peculiarities are always of luetic origin. It may be said, however, that they occur with extreme frequency in congenital syphilitics and that they have so often furnished a clue to a correct diagnosis that their clinical significance can not be overlooked. Such striking results have been obtained by adapting this theory to joint disease. We are not justified in making a diagnosis of tuberculosis in these cases until syphilis has been positively eliminated by the therapeutic test, and, while the author's experience with backache is limited, there is sufficient evidence that backache may in some instances be due to a myositis caused by syphilotoxins to warrant further investigation on the subject.

CHANCRE OF THE FINGERS.—Douglass W. Montgomery, and George D. Culver, San Francisco. Journal of the American Medical Association, 1919, vol. lxxii, p. 180.

If for no other reason than to keep one on the alert in diagnosis, the subject of the primary lesion of syphilis, as it occurs extragenitally, is well worth considering. This is especially true nowadays when the results of early treatment, necessarily dependent on early recognition, are so brilliant, and the consequences of failure to recognize this disease are now known even to the laity as being so portentous. The physician, therefore, in recognizing the true nature of the disease may make a brilliant hit, or in failing to do so may achieve a failure, which from its very nature as appertaining to an eminently chronic malady may continue a reproach during his entire life of practice. The essential difficulty, however, of recognizing these lesions in these situations in their early stages is shown by the cases cited, for one instance occurred in a professional nurse working with a physician, and the other two were in physicians in active practice; yet in no case was the true nature of the disease suspected until the appearance of the eruption.

HYSTERICAL APHONIA ASSOCIATED WITH LATENT SYPHILIS.—Charles Wolf, New York, and E. G. Breeding, Baltimore. Journal of the American Medical Association, 1919, vol. lxxii, p. 639.

From the standpoint of differential diagnosis, the following conditions had to be considered: Acute and chronic laryngitis.—This condition, with the symptoms starting as an acute laryngitis and going into a chronic condition, was thought not probable, as no improvement followed local treatment. Tuberculosis of the larynx.—This condition following an attack of measles had to be considered. The symptoms appeared suddenly, there was no pain, and there was an absence of laryngeal and pulmonary signs, all of which eliminated this diagnosis. New growths.—There was no local or constitutional evidence of these. Interstitial neuritis of the recurrent laryngeal nerve caused by syphilis.—Such a condition causing paresis or paralysis would have responded quickly under specific treatment; there was no improvement in this case. Final diagnosis of hysterical aphonia.—This was made because of restoration of voice after the administration of an anesthetic to an individual who probably had latent syphilis.

SYPHILITIC AORTITIS.—Dr. Roy E. Thomas, Phoenix, Ariz. Southwestern Medicine, 1918, vol. ii, p. 1.

The first 5 to 6 cm. of the aorta are most commonly involved, though in rare cases the abdominal portion is involved. The clinical symptoms of syphilitic aortitis appear late, as a rule, the average time being about seventeen years after the initial lesion. In four cases recently studied the author has found the early symptoms remarkably constant. The patients all complained of dyspnea, especially after eating and upon slight exertion, periods of weakness, substernal pain of burning, dull, or prickling character, and cough. In one patient the cough had been very constant and annoying for more than a year and was entirely relieved after the second dose of diarsenol. Two of his patients noticed voice changes and one felt a pressure at the right of the spine in the interscapular region. Other early symptoms, which have been noted, are palpitation, indigestion, edema and fever. The late symptoms due to occlusion of the coronaries, aneurysm, and damaged aortic valves are too well known to mention here. Certain physical signs may be present in aortitis. These lend considerable aid in diagnosis. Of these perhaps the most constant is a broadened area of aortic dullness, which is said to occur in 40 per cent of cases. Other signs are aortic murmurs, usually double, aortic thrill, moderate cardiac hypertrophy and slightly elevated blood pressure. Other invaluable aids to diagnosis are the Wassermann reaction and the x-ray. In the differential diagnosis of syphilitic aortitis, the only conditions sufficiently common to require mention are arteriosclerosis and rheumatism. A careful history and the age of the patient, together with the laboratory report, will usually be sufficient to properly classify each case. As general propositions it may be stated, (1) uncomplicated aortic regurgitation at middle age is nearly always syphilitic. (2) Any case of cardiac insufficiency occurring suddenly after the fortieth year of age is syphilitic. (3) Any heart lesion, particularly aortic, without a definite history of chorea, rheumatism, or pyogenic infection, but with a history of syphilis or positive Wassermann reaction should be given antisyphilitic treatment. The prognosis of syphilitic aortitis is bad. The irreparable damage done to vital portions of the circulatory system allows us to expect nothing but an early fatal termination from cardiac failure, angina pectoris or ruptured aneurysm. The usual expectation of life after the onset of clinical symptoms is one to two and one-half years.

Syphilitic Aortitis and Its Early Recognition.—George E. Brown, Miles City, Montana. American Journal of the Medical Sciences, 1919, vol. clvii, p. 41.

Analysis of these five cases shows several important points: (1) The frequency with which specific aortitis is confused with pulmonary disease. (2) That specific aortitis is not always a late syphilitic manifestation, as note in Case IV probably six to eight months after infection. (3) That practically all physical signs may be absent and the diagnosis will rest on substernal distress, a positive Wassermann test, and the therapeutic test. (4) That a positive Wassermann reaction means syphilis, and even in the absence of all outward manifestations of syphilis the aorta should be suspected and active treatment instituted. (5) That a negative Wassermann test does not rule out specific aortitis and a luetin test should be performed and the effect of treatment should be studied. (6) That aortitis should be diagnosed before the more gross pathologic changes have taken place, as when that stage is reached, usually treatment is ineffective.

Syphilis and Heart Diseases.—Gaucher, Paris. Journal de médicine, 1918, vol. xxxvii, p. 29.

The domain of visceral syphilis is progressively extending; the majority of chronic affections of the nervous system, some gastric diseases, a larger number of intestinal disturbances, are due to syphilis, either acquired or congenital. The influence of syphilis on the cardiovascular apparatus has likewise been known for a long time past. Aside from affections of the arteries and veins, as well as aneurysms—more particularly aneurysms of the aorta, the invariable syphilitic nature of which is now established—the list of genuine cardiac affections of known syphilitic origin is a lengthy one. At the present day a distinction between syphilitic and parasyphilitic affections (specific in origin but not in character) is no longer admissible, and the term "quaternary syphilis" should replace "parasyphilis;" because in a number of so-called parasyphilitic affections, the causative agent has been found in the form of the parasite of syphilis. In some of these cases, notably in aneurysms, antisyphilitic treatment with mercury and iodide aften exerts a favorable action.

Heart diseases known to be frequently of syphilitic origin are represented in the first place by aortic lesions at the origin of the aorta. Not all aortic lesions are the sequelæ of acute endocarditis sequential to acute articular rheumatism. Careful examination of patients with so-called rheumatic aortitis may reveal partial evidences of tabes, notably the loss of the patellar reflexes. The coexistence of aortic lesions with fully developed tabes is not so very rare and in such association sudden death is liable to occur. Many cases of sudden death from cerebral apoplexy occur in old syphilitics with aortic disease, and some of these are due to embolism. In sudden death we may always suspect syphilis, either from the above mechanism or from perforative myocarditis or angina pectoris. Angina pectoris from occlusion of the coronaries is always of syphilitic nature. Numerous other cardiac lesions have a marked syphilitic factor and even in mitral insufficiency this is beginning to be recognized—although as heretofore rheumatism is regarded as the most common factor. The part played by congenital syphilis is more obscure but is recognized and will prove a fertile field in the future.

PAPULAR SYPHILIS OF THE BLADDER.—Hesse. Correspondenz-Blatt für Schweizer Aerzte, 1918, p. 1146.

The author's case of syphilis of the bladder concerned a young woman of 24 years who was suffering from kyphoscoliosis and gave a tuberculous family history. The patient complained of painful micturition which gradually became aggravated up to severe and frequent urinary tenesmus. The urine contained a considerable amount of pus and at times there was blood but no tubercle bacilli. The suspicion of tuberculosis was not confirmed by the findings of cystoscopy but the peculiar reddish brown hue of the circular papules in the fundus of the bladder and their local bandlike arrangement was suggestive of syphilis. The diagnosis was confirmed by a careful anamnesis, the positive outcome of the Wassermann reaction, and recovery under antisyphilitic treatment.

SYPHILIS OF THE STOMACH.—Bullrich, Buenos Aires. *Revista de la Asociación Medica Argentina,* 1918, vol. xxviii, 555.

An Italian patient, married, aged sixty, was admitted to the de Alvear Hospital on December 11, 1917. He was much emaciated and anemic, with dry and flaccid skin. He was not only extremely deaf, but the mental state was confused and it was quite impossible to obtain a history. His family stated that he suffered with his head, went about alone, especially nights, claiming that he had to visit the privy at frequent intervals. He also complained much of his stomach and bowels. On examination he was found to present few objective evidences of disease and his Wassermann was negative. The objective finds were anemia, the red cells numbering under 3,000,000; absence of HCl in the stomach contents with presence of fermentation acids: occult blood in the feces. The radiogram of the stomach suggested the possibility of cancer. But despite the negative Wassermann it was thought wise to give an inunction cure, which had a most unexpectedly favorable outcome. The weight and blood count rapidly improved. The HCl did not, however, return to the stomach and the radiogram which had shown originally a marked downward displacement of the viscus with a suggestion of perigastritis underwent no change. The diagnosis of syphilis of the stomach was therefore made by exclusion and by the success of the specific treatment.

Syphilis of the Stomach.—Dasso, Buenos Aires. *Revista de la Asociación Medica Argentina,* 1918, vol. xxviii, 610.

The author was consulted by a steward of a ranch, single, age forty-two, who wished to be operated on for gastric ulcer, the actual indication being alarming hemorrhages from the stomach. He had acquired syphilis at the age of thirty and had undergone an incomplete mercurial cure. For the past two years he had suffered from dyspepsia, the most conspicuous early symptom of which had been hyperchlorhydria, which appeared in paroxysms and was controlled by sodium bicarbonate. After several months he began to complain of pain in the stomach aggravated by food and eventually vomiting of blood as stated. The patient was placed on mercury injections and an ulcer diet, and made a good recovery. The author saw a second case in a man of twenty-eight with history of syphilis who had suffered with his stomach for three years—gastralgia and pyrosis with muscular rigidity at the epigastrium. On account of the intensity of the symptoms it was thought best to intervene surgically, and a gastroenterostomy was performed for what proved to be a juxtapyloric ulcer. A few injections of biniodide cleared up the residual pains in the stomach. In any gastric ulcer today it is necessary to take account of the patient's antecedents in respect to syphilis.

Syphilis of the Tongue.—George D. Culver, San Francisco, Cal. Journal of Cutaneous Diseases, 1919, vol. xxxvii, p. 48.

Among 530 instances of syphilis seen in private practice, the tongue was involved in 27 (5.09 per cent). There were 62 cases with mouth involvement, not including instances of syphilitic angina. Therefore, the tongue was affected in nearly one-half of the mouth cases, and in the greater proportion of the lingual cases the disease was limited to the tongue. Of these 27 cases, 23 were males and 4 were females. There was one instance of lingual chancre, 9 instances with mucous patches, 8 with gumma, 9 with chronic specific glossitis, including leucoplakia, 4 having leucoplakia associated with other phases of chronic specific glossitis. The single instance of chancre of the tongue occurred in a girl; it was one case in 27 extragenital chancres; it was situated on the dorsal surface near the median line, 2 cm. from the tip; and it had been present ten weeks, healing slowly and unrecognized until after the development of florid secondaries. Though lingual chancre is comparatively uncommon, the diagnostician should not fail to recognize the lesion when it does occur. If he considers the possibility he need have little difficulty in proving the diagnosis. The nine instances of mucous patches on the tongue were in a group of 21 cases with buccal mucous patches, in which forty-three locations were involved. Six males and two females had lingual gummata. In all these eight cases the shortness of duration was striking. They ranged from one-half month to six months, an average of two and one-half months, indicating that a gumma on the tongue as elsewhere in the oral cavity grows rapidly. One may account largely for the short average duration of time preceding consultation by the fact that the patient considers such a lesion in this location seriously, and seeks treatment early. All the patients who had gummata with but one exception gave positive histories, and in only one was there a negative Wassermann reaction. The one with a negative Wassermann reaction gave a distinct history of having had syphilis. Judging from these facts, it should not be difficult to determine when antisyphilitic medication is indicated. In one of the four instances in which leucoplakia was present it was of especial interest. The patient was a young man, aged 22, whose tongue in addition to presenting the distinct leucoplasic patch, had further evidences of chronic specific glossitis in the form of a sensitive opalescent edge with infiltration and slight fissuring. There was a markedly positive Wassermann reaction of the blood serum. The patient gave a history of a sore acquired at sixteen years of age. He had a strong impression that the leucoplakia antedated this by two years, but he may have been in error. The leucoplakia was eradicated with radium. There are many characteristics of chronic specific glossitis which make this form of syphilis stand out distinctively. Nine patients, one-third the entire number of syphilitic tongue cases, sought relief for this affection. Eight were males. A long enduring syphilitic glossitis may present a composite picture. On the dorsum may be seen areas of induration with cicatrices adjoining, depressed opalescent spots, sodden epithelial surfaced areas, others bald of papillæ, fissuring, soft nodules singly or in groups, and irregular leucoplasic patches of glazed appearance or thickened to a leathery or even wart-like surface. As characteristic as any feature is the markedly sensitive edge of the tongue on both sides or more frequently limited to one side. One of the most important conclusions reached is that with a doubtful tongue lesion it is not only a justifiable procedure, but it is urgently advised to administer an infusion of arsenobenzol as a therapeutic test even though the Wassermann reaction prove negative.

FRAMBOESIFORM SYPHILIDE.—W. McMurray, and Langloh Johnston, Medical Journal of Australia, 1918, vol. ii, p. 306.

S. L., aged 49, a Dalmatian, residing in this country for the last fourteen years, gives a history of having coitus four months ago. There are two abrasions on the penis, one on the dorsum of the balanopreputial fold, and the other on the frenum. The glands in the groin are not affected, but the glands in the axilla are enlarged. On the chin there are three sessile tumors, the largest being the size of a shilling. Two partly coalesce and project abruptly about a quarter of an inch above the surface. The surface of each is light red color, granular, and devoid of hair, except at the margin, where it is loose. The tumors have attained this size in six weeks. In the mouth at the commissure of the lip on the left side is an ulcerated surface and a mucous patch is present under the tongue. There are no other syphilides in any other part of the body. Spirochetes have been sought for, but none have been found. The Wassermann reaction is positive.

SYPHILIS AS IT PERTAINS TO THE EYE.—Albert E. Bulson Jr., Fort Wayne, Ind. Journal of the Indiana State Medical Association, 1918, vol. xi, p. 438.

The eyelids are especially prone to be affected by syphilis. The disease may occur either as a primary sore, or as a secondary or hereditary manifestation. Inflammation of the tarsus, presenting great thickening of the tarsus, and not uncommonly found in children, is usually syphilitic in origin. Syphilis of the conjunctiva may be manifested by chancres which may occur on either the palpebral or ocular conjunctiva; but a more common manifestation of syphilis is the papillary syphilides, and especially the syphilitic conjunctivitis which appears as a stubborn catarrh, or in the form of granulations, similar to trachoma follicles, in an anemic conjunctiva. One of the most common ocular lesions of syphilis is interstitial or parenchymatous keratitis, in which a chronic thickening of the whole cornea takes place. It occurs most frequently between the ages of five and fifteen years, occasionally as early as the third year, and rarely after the thirtieth year. Interstitial keratitis of acquired syphilis is usually a late secondary or tertiary lesion, and usually it appears in adults between the twentieth and fiftieth year of life. It is more promptly amenable to treatment. A troublesome inflammation of the eye which has a tendency to run a chronic course, and very often due to syphilis, is what is known as scleritis, which occurs as a diffuse bluish-red injection of the sclera, very painful, unattended with secretion, and liable to be mistaken for conjunctivitis or iritis. Iritis is a manifestation of syphilis in a very large percentage of cases. It may appear between the second and ninth month after the initial lesion, or may be delayed until the eighteenth month. Occasionally it may appear as a tertiary manifestation, either as primary iritis or as a gumma of the iris. An ocular affection which may produce great disturbance of vision, and is aften unrecognized until well advanced because of the absence of pain and external evidences of inflammation, is chorioiditis. In a very large percentage of cases chorioiditis is due to acquired syphilis, and it appears from six months to two years after the initial infection, though sometimes it is postponed to the tertiary period. Syphilitic retinitis in its various forms, including the types with exudation as well as those with hemorrhages and degenerative changes, is relatively common, and may be due to congenital or acquired syphilis. A rather common syphilitic ocular lesion is a paralysis of one or more of the extrinsic muscles of the eyeball. It is generally one of the later manifestations, but it has been noted as early as within six months of the primary infection, particularly in the form of ptosis. In rare instances paralysis of the ocular muscles results from inherited syphilis. Periostitis of the orbit, particularly in its chronic form, with deep seated pain, usually worse at night, tenderness on pressing the eyeball backward, thickening of the tissue beneath the orbital margin, and perhaps some inflammation of the eyelids and conjunctiva, is most often a late manifestation of syphilis. In general it may be stated that a syphilitic basis for the ocular lesion is diagnosed not only by certain features of the lesion itself, but by the presence of lesions in other parts of the body, or physical characteristics, and by the results of the Wassermann test. However, one must not be led astray by a negative Wassermann, as negative Wassermanns are not infrequent even in the presence of syphilis, and this is particularly true in the presence of inherited syphilis, and to a less extent in the tertiary lesions of syphilis.

Report of Interesting Nasal Cases Probably Due to Syphilis.—Dunbar Roy, Atlanta, Ga. Journal of the Medical Association of Georgia, 1918, vol. viii, p. 137.

Of the certainty of diagnosis there, of course, may be some difference of opinion, but the results obtained by the use of the iodide of potassium would rather indicate the specific nature of the affection. The writer believes that there are many lesions in the nasal cavities which have their dependence upon syphilis. It is not always necessary to look for ulcerations and even destructive processes in order to have a picture of nasal syphilis. Manifestations of specific lesions in the nose resemble many other affections and the fact that we sometimes get such poor results in intranasal operations may have its real cause in a failure to recognize a constitutional systemic dyscrasia which in one word is syphilis. The rhinologist who waits for typical textbook pictures of lesions or is entirely dependent upon clinical tests will fail in many instances to bring about a successful result. The obscure ramifications of the syphilitic virus are manifold in character and we can never be too diligent in instituting antispecific treatment if no other cause for the condition can be found. Congestion and edema of the nasal mucous membrane as is sometimes found in the early stages of syphilis very frequently resembles those cases of vasomotor rhinitis in all of its manifold symptoms.

UNSUSPECTED SYPHILIS AND PREGNANCY.—Boero, Buenos Aires. Revista Espagnola de Sifilis per Revista Medica Cubana, 1918, vol. xxix, p. 464.

At the author's maternity clinic 900 parturients were interned during the first five months of the year and of this number no less than 229 presented from first to last symptoms which caused suspicion of syphilis; as a result of which they were submitted to Wassermann tests. The result was a surprise, for but 106 of the number gave a positive result. There were 10 who showed only a retardation of hemolysis while in 113 the reaction was frankly negative. These figures show the untrustworthiness of the negative Wassermann, and also show that while this reaction is of great value in uncovering concealed syphilis it is very misleading when it aids in the suppression of clinical syphilis. The clinical manifestations of the disease are innumerable, and while by itself a symptom proves nothing, cumulation of a number of symptoms is a very different proposition which can not be disregarded. If we add to the number of syphilitics unmasked by the Wassermann alone, the clinical cases which are presumably syphilitic despite the negative Wassermann, it appears that for every one hundred individuals—the writer is speaking of Buenos Aires specifically—from 20 to 25 are spirochete carriers of some sort. The more the subject is studied the more evident is the conviction that in all chronic disease we must begin by excluding both tuberculosis and syphilis. It is unnecessary here to go into the infinite number and variety of symptoms of syphilis in the family and kin, the parents, the childbearing woman and her pregnancies, the newborn and its subsequent development, the other children of the marriage, etc. For while one symptom may, as already stated, prove nothing, the cumulation of evidence from the most varied sources, duly weighed, can not be disregarded and is at least as valuable in diagnosis as a negative Wassermann.

HYPOPHYSARY INFANTILISM AND SYPHILIS. Lereboulet and Mouzon. Revue de Neurologie, 1917, vol. xxiv, p. 493.

Syphilis should be kept in mind—as was emphasized by the authors on the basis of a personal case—among the causes of hypophysary infantilism. The specific infection may act through the intermediation of osseous lesions of the sella turcica, or it may reach the hypophysis through inflammatory meningeal processes, which was probably the mechanism in the authors' case, in a male subject aged twenty-three years who had the appearance of a child. He was brought to the hospital by his mother for visual disturbances and retarded development. The condition was found to be one of practically pure infantilism due to arrested development with but few traces of obesity. The genital organs were found to be not only infantile but atrophic, the right testicle having the size of a pea, while the left was imperceptible. The pubic region was absolutely smooth and hairless. The patient appeared to be about 13 years old in stature and facial expression. He presented no sign of dysthyroidism and no evidence of feeble-mindedness. There was bilateral optic atrophy and left temporal hemianopsia. Notwithstanding the absence of well-defined urinary disturbances and the negative outcome of radiography, there could be little doubt as to the hypophyseal origin of the symptoms presented by the patient.

A CASE OF TRAUMATIC SYPHILITIC GUMMA.—Levy and Gely. Journal de médécin de Paris, 1918, vol. xxxvii, p. 134.

In the case reported by the authors the clinical and microscopic finds and therapeutic results all pointed in the same direction. In all such cases the external violence plays the role of a local rather than a determining cause. As a rule the subject suffers from tertiary syphilis. The author's patient was an aviator, aged twenty-five, who in an unfortunate landing suffered a severe contusion in the shoulder and clavicular region, without wound or fracture, as shown by the negative x-ray. The treatment consisted of massage and progressive mobilization. After ten days of treatment the flyer returned to his service and did not complain until the expiration of a week, when an apparent abscess made its appearance in the clavicular region. A swelling the size of a walnut with indurated and non-adherent base and dark red, agminated center was noted at the junction of the outer and middle third of the clavicle, at the level of the lower border of the bone. The center of the swelling was the only point in which softening was apparent and by the next day the skin had given way to the extent of one square centimeter. The oval ulceration presented sluggish, slightly ragged and not very adherent margins. The floor was free from pus, but there was some oozing under the crusts. The base of the tumor retained its hard consistence, suggesting an ulcerated gumma. This view was confirmed by the history of a chancre of the penis in 1914 (although this lesion had not been regarded as specific nor had it been treated specifically). There had been no mucocutaneous manifestations or headache or pain in the bones—in other words no secondary manifestations. But the spirochete was present in large numbers in the scrapings of the gumma. Under the old mixed treatment—mercury and potassium iodide—wonders were accomplished, the treatment causing the gumma literally to melt away in a few days. Healthy granulations appeared and the wound healed in three weeks.

ASSOCIATION OF SYPHILITIC CHANCRE AND VINCENT'S ULCER.—Payenville. La Presse Médicale, 1918, vol. xxvi, p. 647.

A woman appeared at the author's clinic with an ulcer of the labium majus of one side. This was covered with a diphtheroid membrane and accompanied by inguinal adenopathy. Its duration was nearly one month. A smear placed under the ultramicroscope showed Vincent's spirillum and fusiform bacillus but no treponemata. Much astonished was the author when he obtained a total positive Wassermann. He became convinced that his spirochetic technic might have been at fault. The ulcer after treatment for twenty-four hours with moist dressings of boiled water was again examined and smears showed the presence of numerous treponemata. The lesson is that our routine technic for the spirochete is defective. A special process is able to demonstrate the presence of both the treponema and the organisms of Vincent in the same smear. This involves the use of colloidal silver as a substitute for other dark stains, according to the method of Harrison. The background is a light mahogany upon which field all of the organisms appear white and are easily recognized by their contours.

JUVENILE PARESIS—A BRIEF REVIEW WITH REPORT OF CASES.—Leon Emile Duval, Washington, D. C. Alienist and Neurologist, 1919, vol. xl, p. 33.

The primary manifestations of the disease, like those in the adult type, are apt to take the form of changes in the personality, morals and character of the individual. Upon these changes is engrafted a gradual progressive dementia. About one-half of these children are backward or actually feeble-minded, and as the first symptoms may be convulsive seizures, these patients are not infrequently admitted to epileptic colonies or other institutions with the diagnosis of epileptic imbecility. The other half are normally bright, and show normal development, though many of them begin to show some intellectual deterioration about five years of age. Often they do well in school, and show normal adjustments in every way. At or before puberty, they begin to show signs of deterioration. In those cases in which the onset occurs after puberty, we note that there are few manifestations of the development of sexuality. Female children fail to menstruate in many cases. Masturbation is rather common among these individuals. Infantilism is by no means uncommon. A previously good natured child becomes surly, morose, indifferent, careless, wanders away from home, is forgetful, and gives up its occupation. Strange and unusual behavior may first attract the attention of the parents. Gradually other signs of mental deterioration present themselves. Apathy, indifference, marked hebetude—or perhaps extreme silliness of demeanor—become features of the case. Asocial acts are uncommon, in contrast to the adult type. Delusions and hallucinations are also uncommon, and the parents often see no change until the child becomes untidy in its habits. Delusions of wealth, grandeur, and the like, occur only in adolescents, because ambition and the sexual passions do not dominate the will until puberty. Convulsions are frequent and often severe, and bear no relation to the prognosis, as the child may live for years after the beginning of convulsions. Paresis is, of course, a common symptom. They do not differ from those of the adult type. The usual course of the disease is that of gradual deterioration, which becomes extreme, as these cases live for many years.

ERRORS OF DIAGNOSIS IN PRIMARY EXTRAGENITAL SYPHILITIC LESIONS.—Marcel Pinard, Paris. Boston Medical and Surgical Journal, 1919, vol. clxxx, p. 242.

A soldier had occasion to consult the medical officer of the district where he was staying for considerable glandular enlargement under the chin. The condition was diagnosed as "goiter" and an operation was judged necessary. The patient narrowly escaped being operated upon, his exemption being due to the intercession of an army surgeon, who noticed that he had a secondary eruption. It turned out to be a case of syphilitic chancre of the mouth with tremendous enlargement of the glands. Another soldier, while being shaved bled under the chin. He was dressed at the infirmary, where it was thought to be a mosquito bite. He complained of pain on swallowing, and aphonia, and he went to a hospital for a month. As he was anxious that his tonsils should be removed, he was sent to the throat clinic, where syphilis was diagnosed, and he was dispatched to a center for syphilis, two and a half months after the appearance of the primary lesion. A third patient was transferred with the diagnosis, "glandular abscess of the left axilla." He was admitted to the surgical ward, when he was suffering from sore throat, with high fever, severe nocturnal headache, and albuminuria. Papuloerosive lesions were discovered on the sheath and scrotum. The diagnosis of secondary syphilis could not be called in question. A fourth patient, employed in a munition factory, was sent by his doctor to the dermatologic clinic on account of a cutaneous eruption. It proved to be a maculopapular secondary syphilitic eruption. Search was made for the primary lesion, which was neither in the throat nor in the genitals. A dressing on the right thumb led us to suspect that origin, and as a matter of fact an ulcer was found there that had existed since two months, depressed, irregularly oval, not punched out, with a red muscular floor, slightly infiltrated. No epitrochlear adenitis, but some enlargement of the axillary glands. Wassermann reaction strongly positive. These several cases show the importance for the practitioner of being prepared to diagnose extragenital syphilis. The chancre itself, as well as the glandular enlargement, might pave the way to very unnecessary surgical interventions, and open the door to further infection, not to speak of the consequence to the patient of having no proper treatment for many weeks or months.

STRIAE SYPHILITICA.—Albert Abrams, San Francisco. Medical Review of Reviews, 1919, vol. xxv, p. 11.

In presenting a new cutaneous sign, the writer requests the reader to recall the lineæ albicantes atrophic lines or streaks observed in the abdominal skin after stretching from pregnancy, obesity, tumors, ascites, etc. In syphilis as in other diseases one finds in every individual definite areas of dullness. Inspection of these areas in a suitable light shows them to be surrounded by a faint white line (made more evident by stretching the skin). They are more evident and diagnostic over the lung areas owing to the many factors which produce striæ on the abdominal skin. On the thoracic skin they may be found on both sides, but always more conspicuous on the right side in syphilis. In some instances the lines are pigmented. The lines in question not unlike the "glossy skin" are of trophic origin and to explain them one must recall the writer's electronic conception of symptomatology.

DIAGNOSTIC DEMONSTRATION OF SPIROCHETA PALLIDA.—Herman Goodman, New York. Interstate Medical Journal, 1919, vol. xxvi, p. 61.

Wipe the surface of the lesion with a cotton sponge, using a little pressure. This removes the superficial epidermal debris and many confusing saprophytic spiral organisms. Rub the denuded surface briskly or tease it with a needle, scalpel, or other instrument very lightly, being careful not to get any appreciable bleeding. Squeezing the lesion between two fingers after surface cleansing may furnish sufficient serum without having recourse to any of the above aids. As soon as enough serum collects on the surface of the lesion, transfer either to the slide or cover slip, directly or by a platinum loop. Use only thin slides and slips that are new and free from any scratch marks. Perfectly clean slides and slips are a source of considerable satisfaction. Have a drop of immersion oil both on the under surface of the slide and on the upper surface of the cover slip. This insures a continuous airless medium from dark-field to objective. Lower the oil immersion objective into the oil, almost touching the cover slip. Do not have it touch, because, if the serum is scanty and the oil thick, you are likely to raise the cover slip from the slide. Focus with the fine adjustment until you see the dark background, in which glistening dancing particles move among perfect white rings of light. The small particles are minute ultramiscroscopic organisms and colloidal bodies of the blood serum. The rings are the outlines of red blood cells. When this field has been obtained, search for the gleaming, twisting spirochetes. The objections to the India-ink method are numerous. Among others, mention is made of the greater difficulty of finding even in a well-made smear a still object as compared to a motile one. In cases where the lesion has few spirochetes the India-ink method is far inferior. The making of the smear and changes in osmotic pressure so contorts the spirals that the task of differentiation of pathogenic and nonpathogenic spiral organism is increased. At this time the impossibility of securing the foreign Chin-Chin puts this method beyond the pale of good usage; the only substitute, a commercial India ink, already contains spiral organisms or spiral-like artefacts.

The Early Diagnosis of Syphilis.—Joseph V. Klauder, Philadelphia. Journal of the American Medical Association, 1919, vol. lxxii, p. 693.

To prevent the spread of syphilis and to insure a cure, it is imperative that the diagnosis be made at the earliest possible moment. The average duration of the genital chancre in this series of 115 cases was 34.4 days. A secondary eruption of syphilis was present in 24.7 per cent. Local treatment had been applied to the chancre in 66 per cent. The means at our disposal for the early diagnosis of syphilis are the dark-field apparatus, the Wassermann reaction, and clinical evidence. A positive dark-field examination was obtained in 57.1 per cent of this series. The shorter the period from the appearance of the chancre, the more likely it is that the dark-field examination will be positive. The converse is true with the Wassermann reaction. Therefore the dark-field apparatus is not only the preferable laboratory test, but it is also more successful than the Wassermann reaction in the diagnosis of early syphilis. The too common practice of treating genital chancres with a spirocheticidal drug before they are properly diagnosed may prevent or greatly delay the obtaining of a positive dark-field examination. A positive Wassermann reaction was obtained in 74.1 per cent of this series. This reaction in late primary syphilis is the most successful laboratory method for diagnosis. Both laboratory tests were negative in 8.6 per cent. Therefore, by the use of both tests, 91.4 per cent of the chancres in this series were diagnosed by laboratory methods alone. However, by the use of these tests alone, delay may be experienced before the spirochetes are found in the secretion from the chancre, or before the Wassermann reaction, if negative, becomes positive, or before the report of this test is obtained. Treatment is therefore delayed, and delay at this time may be fatal and may mean an involvement of the nervous system. Moreover, if a chancre is seen in the negative stage of a Wassermann reaction, and if the dark-field examination is negative, it is not ideal to await the appearance of a positive Wassermann reaction for diagnosis. A definite clinical diagnosis of a genital chancre can often be made. If a genital sore is clinically a chancre, and if the dark-field examination and the Wassermann reaction are both negative, it is perhaps better to start intensive treatment rather than await the appearance of a positive Wassermann reaction.

A STUDY OF COMPLEMENTS USED IN THE WASSERMANN REACTION.—E. H. Ruediger, Bismarck, N. D. Journal of Infectious Diseases, 1919, vol. xxiv, p. 120.

The complements of fresh guinea pig serum varied greatly in fixability. While one complement gave six-plus with a certain human serum another complement gave only three-plus with the same serum, other things having been equal. Another serum gave three-plus with one complement and one-plus with another complement. This variation in fixability was not due to complement alone, when a complement showed poor fixability with a certain human serum the same complement was well fixed by other human serums. A mixture of five complement serums gave fairly uniform results. These results show clearly the unreliability of a single complement serum. Human complement gave much weaker positive results than did guinea-pig complement. Noguchi's recent method of doing the Wassermann reaction gave negative results with serum that was known to be from syphilitic persons and gave six-plus by our regular method. Normal human serum giving six-plus result with the Wassermann reaction, on testing them again twenty-four hours later negative results were obtained while controls which were diluted similarly with salt solution gave positive results. Neutralization of complement-fixing power by normal human serum or by guinea pig serum progressed fairly rapidly, 50 per cent was neutralized in two hours. At the end of four hours neutralization of complement-fixing power was sometimes complete, especially by guinea pig serum, which was a trifle more effective than the human serum. A neutralization test of this kind may become of value in detecting syphilitic serum which no longer gives a positive result by the Wassermann reaction alone. Future observations must determine its value. Guinea pig complement left on the clot and kept in the refrigerator remained fairly constant for three days, while complements which had been removed from the clots deteriorated more rapidly. Deterioration took place in two directions, the complement lost fixability and it lost the power to reactivate the hemolytic amboceptor. Complements with which six-plus was obtained about twenty-four hours after bleeding gave negative results with the same human serums six days later. Fixability disappeared more rapidly than did the power to reactivate hemolytic amboceptor. Ramy's method of preserving complement by sodium acetate was a total failure in the author's hands. Fresh guinea pig serum mixed in proportion of 4:6 with a 10 per cent solution of sodium acetate in salt solution began to deteriorate immediately. In three days it lost about 33 per cent fixability while the control portion to which no preservative had been added remained constant. Although deterioration of preserved complement began earlier than that of the control it progressed somewhat slower. Glycerol seemed to prevent deterioration of complement for a few days. In complement preserved by glycerol fixability increased during the first three days and on the seventh day it still was nearly equal to the fresh serum.

A Comparison of Six Different Antigens in the Wassermann Reaction.—E. H. Ruediger, Bismarck, N. D. Journal of Infectious Diseases, 1919, vol. xxiv, p. 31.

Antigen diluted with the salt solution slowly so as to give an opalescent solution gave many more positive results with the Wassermann test than did antigen which was diluted rapidly enough to give a clear solution. Adding the antigen to the human serum before the complement gave results identical with those obtained when the complement was added before the antigen. Antigen supposed to be alcoholic extract of syphilitic fetal liver and antigen prepared from dog heart gave many more positive results than did alcoholic extract of human heart. As no other signs or symptoms of syphilis could be detected these were considered false positive results, and these antigens discarded as being unreliable. Antigen prepared from sheep heart gave results almost identical with those given by antigen prepared from human heart. The glycerol added to the human serum can not be held responsible for the false positive results obtained. Previous absorption of the natural antidog amboceptor from the human serums did not eliminate the false positive results.

Further Observations on Antigens Used in the Wassermann Reaction.—E. H. Ruediger, Bismarck, N. D. Journal of Infectious Diseases, 1919, vol. xxiv, p. 204.

With serums from 50 clinically nonsyphilitic persons alcoholic extract of human heart, alcoholic extract of beef heart, and alcoholic extract of rabbit heart gave negative results. Alcoholic extract of dog heart gave positive results with 16, or 32 per cent, and alcoholic extract of guinea pig heart gave positive results with 17, or 34 per cent, of these serums from clinically nonsyphilitic persons. As no other signs or symptoms of syphilis could be discovered, these were considered false positive results, and heart of dog and of guinea pig are considered unsuitable for the preparation of so-called antigen to be used in the Wassermann reaction. Whenever the alcoholic extract of dog heart gave a positive result the alcoholic extract of guinea pig heart also gave a positive result; the latter usually reacted somewhat stronger than did the former. With serum from known syphilitics the alcoholic extract of beef heart and the alcoholic extract of rabbit heart frequently gave stronger positive results than did the alcoholic extract of human heart. The results obtained with alcoholic extracts of dog heart and guinea pig heart corresponded to those obtained with alcoholic extract of human heart, while the alcoholic extract of sheep heart reacted weaker. When antigen was added fifteen minutes after the complement, the same results were obtained as when antigen was added fifteen minutes before the complement. Antigen dilutions of 1:35, 1:45, 1:50, and 1:75 gave results that were identical with those given by a dilution of 1:25. Dilutions of 1:100, 1:200, and 1:300 gave irregular results, sometimes stronger, sometimes identical with, and other times weaker than, those given by a dilution of 1:25. Dilutions higher than 1:300 usually gave weaker positive results than did the dilution of 1:25.

A MODIFICATION OF THE WASSERMANN TEST.—Clarence N. C. Callary, Philadelphia, Pa. Journal of Laboratory and Clinical Medicine, 1918, vol. iv, p. 140.

The author maintains that Wassermann's original method is subject to an error arising from the presence in human serum of a varying amount of natural antisheep amboceptor. An excess of amboceptor might result in complete hemolysis in a test, if a small fraction of the complement were left unfixed by the syphilitic antibody. Another result of an excess of amboceptor would consist in a partial dissociation of the complement from its combination with the antigen-antibody compound. Human serum contains a certain quantity, and sometimes a large quantity, of amboceptor hemolytic for sheep red cells. From these considerations it follows that the serum from the patient must, in each case, be titrated in order to determine the hemolytic unit. For this purpose a number of mixtures are made in test tubes, containing each 0.1 c.c. of serum of patient (inactivated at 54° C. for 15 minutes), 0.2 c.c. of a 20 per cent complement (fresh guinea pig serum) and increasing quantities of a 5 per cent emulsion of sheep's red cells. These tubes are placed in water-bath at 40° C. for one hour and following this, there are added to the test the required quantities of a 5 per cent emulsion of sheep's red cells (2 units) and test is again placed in water-bath at 40° C. for one hour, when the final reading is made. In a given case titration tube No. 3 (0.4 c.c. of a 5 per cent sheep's red cells) represents one unit, and one-half, or 0.2 c.c. of a 5 per cent emulsion of sheep's red cells, two units, are the quantities to be used for the test tubes 6 to 9. In 10 per cent of human serums in which no amboceptor is present to complete test, add one unit of amboceptor (that has been titrated with 0.2 c.c. of a 20 per cent complement against 0.5 c.c. of a 5 per cent emulsion of sheep's red cells).

THE WASSERMANN REACTION IN AN ANTICOAGULANT MEDIUM (OXALATED PLASMA).—Benard. Comptes Rendus des Séances de Société de Biologie, 1918, vol. lxxx, p. 334.

The complement is present in the blood which has been rendered noncoagulable by the addition of potassium oxalate. The addition of its own volume of potassium oxalate solution to blood does not modify the outcome of the Wassermann reaction. After centrifugation the plasma can be utilized without heating or after inactivation, to carry out the reaction. The findings are the same as with the serum, as shown by numerous comparisons with the customary serum methods. Only in a few exceptional cases, plasma heated to 56° C. yielded a slightly less complete reaction than the heated serum.

POSITIVE WASSERMANN REACTION IN TWO CASES OF TUBERCULIDES.—Schaumann. Annales de Dermatologie et de Syphiligraphie, 1918-19, vol. vii, p. 8.

The cases occurred in subjects aged, respectively, thirty and thirty-eight years. The tuberculides were of the papulonecrotic type. Ordinarily this behavior would mean one of three things—tuberculides simulating syphilides, tuberculides complicating latent syphilis and aberrant Wassermann. Syphilis of any form, including congenital infection, seemed to be excluded by the total absence of any history or stigmata or collateral manifestations pointing to that affection and by the therapeutic test, since mercurials were of no benefit and in one case the lesions became aggravated under their use. It may, of course, be denied that the positive Wassermann was caused by the presence of the cutaneous lesions. The reaction was pronounced and we have either to assume that it was aberrant or that syphilis, if present, was of a type refractory to antisyphilitic treatment.

THE VALUE OF THE WASSERMANN REACTION IN PREGNANCY.—Edward L. Cornell and A. W. Stillians, Chicago. Journal of the American Medical Association, 1919, vol. lxxii, p. 551.

The first series of private cases of pregnancy gave only 3.6 per cent of positive Wassermann reactions. The second series of charity cases gave nearly 10 per cent of positive reactions. More than one third of these positive cases were detectable only by the serum examination. Routine Wassermann reactions in pregnancy are amply justified by these findings. A surprisingly large number of apparently nonsyphilitic women give a history of frequent abortions. The Wassermann reaction should be checked by searching for the spirochete and by postmortem examinations when possible.

THE NATURE AND INTERPRETATION OF THE COLLOIDAL GOLD REACTION. —Karl M. Vogel, New York. Archives of Internal Medicine, 1918, vol. xxii, p. 497.

It must be emphasized that each of the different tests on the spinal fluid is of value only as a single factor in the entire examination, and that no one test alone is pathognomonic. The colloidal gold reaction is the most sensitive indicator we have of pathologic changes in the spinal fluid, the globulin reaction closely approaching it in delicacy. Uremia, neurasthenia, serous meningitis, hemiplegia and chronic alcoholism may give a cure in the syphilitic zone. If the gold reaction is negative, it is highly probable that the spinal fluid Wassermann will also be negative. An important application of the gold reaction is in the recognition of the earliest stages of cerebrospinal syphilis, and its routine employment in all syphilitics is to be recommended as an aid in the prophylaxis of the parasyphilitic diseases.

THE CEREBROSPINAL FLUID IN THE DIFFERENT STAGES OF SYPHILIS.— Cornaz, Lausanne. Correspondenz-Blatt für Schweizer Aerzte, 1918, vol. xlviii, p. 1584.

The author's conclusions are as follows: he can do little more than confirm the finds of his chief, Professor Dind, published in 1914. In about 35 per cent of hard chancres there is already evidence of the participation of the meninges in the increased number of lymphocytes, even before the first outbreak of the disease in the skin and mucosæ: or more strictly speaking before we can demonstrate its presence in these structures. In the spinal fluid it is the lymphocytosis which first betrays the presence of the disease at a time when the albumin content is still normal and the Wassermann negative. During the exanthematous period a complement fixation can be obtained in the spinal fluid in 14 per cent of cases and about the same percentage is found if early mucous lesions are present in the shape of broad condylomata. In ordinary mucous patches the percentage is as low as 4. We are fully in the dark as to this behavior, but a good hypothesis is that which makes of the broad condyloma a cutaneous lesion in distinction from the mucous patch proper. Hence the broad condyloma may be of the nature of an allergic phenomenon, the latter, as shown by Dind, being peculiar to the skin. Once localized in the central nervous system syphilis tends to persist therein, whence the necessity of testing the cerebrospinal fluid at intervals by the means in our power. The author seeks to impress upon the casual reader the importance of lumbar puncture in early syphilis. In several hundred cases of this little operation he has not seen a single untoward result of a serious character. He would not withdraw over 5 c.c. which is sufficient for the lymphocyte count in Nageotte's chamber, the albumin test and the Wassermann.

STUDIES ON THE DIFFERENT REACTIONS (LYMPHOCYTOSIS, BISGAARD, ROSS AND JONES, AND WASSERMANN) IN THE CEREBROSPINAL FLUID IN CASES OF SYPHILIS.—Carl With, Copenhagen, Denmark. Brain, 1918, vol. xl, p. 403.

The author thinks we may safely regard a cell count of 4 or less than 4 as normal, and a count between 4 and 10 as suspicious of a pathologic process, and a cell count greater than 10 as definitely pathologic. In regard to the Bisgaard-Ross-Jones reaction if we exclude patients suffering from dementia arteriosclerotica and disseminated sclerosis we arrive at the result that a material of about 150 ''control'' cases showed an ammonium sulphate value generally one or less, but sometimes as great as two: the nitric acid value is generally fifteen or less, fairly often twenty, and in a few instances twenty-five. The author's observations confirm the general view that lymphocytosis is rare in cases of cerebral tumor, and of spinal tumor. In eighteen patients, in whom the diagnosis was certain, the highest cell-count was 3 per cubic centimeter, and even if the five patients in whom the diagnosis was somewhat doubtful be all included the highest value is 6.7 per cubic centimeter. Thus among 23 cases a definite lymphocytosis was never found. The finding of a pathologic value of Bisgaard-Ross-Jones in the absence of any increase in the cellular count is comparatively rare in syphilis, hence the absence of lymphocytosis in a specimen of cerebrospinal fluid which contains an increased amount of protein has some diagnostic value. The author's material is too small to allow him to form any definite judgment upon the alleged power of salvarsan to provoke the various reactions in the cerebrospinal fluid, nevertheless it struck him that several of his cases gave evidence of such an effect. Among the 82 cases of primary syphilis which the author has examined, one of the reactions showed pathologic changes in 6 cases (7.4 per cent), and in eleven other cases the fluid was not quite normal (13.4 per cent). Twelve of these 82 cases had been treated previously with salvarsan, and of these 12 cases, in 6 the fluid was more or less pathologic. On the other hand, in 6 out of 72 cases which had not been so treated similar pathologic changes were present. These results, therefore, tend to support Gennerich's hypothesis, that salvarsan has a provocative influence upon changes in the cerebrospinal fluid in cases of primary syphilis. Seeing that apparently characteristic soft chancres later on often take on syphilitic character, and as, moreover, the correct diagnosis and proper antisyphilitic treatment is often delayed on account of a previous treatment with, e. g., iodoform or carbolic acid, it has been proposed (cf. Hugo Muller) to treat all soft chancres with injections of salvarsan. The facts detailed above are certainly in favor of this mode of treatment and certainly in each individual case this question ought to be considered. Soft chancres should be regarded as manifestations of serious disease, and for a long time the patient should be regarded as a potential syphilitic and the Herman-Perutz and the Wassermann tests should be applied at least several times; and, if possible, the cerebrospinal fluid should be examined in all patients suffering from an inguinal bubo, at least when they are in-patients at a hospital. The author has examined the cerebrospinal fluid of 134 patients (55 men and 79 women) at the time of the first secondary syphilitic eruption. The majority of these patients had received no treatment or at most had received only a few inunctions of mercury. In fifteen cases, comprising 6 men and 9 women, the cerebrospinal fluid showed pathologic alterations (10.9 per cent men and 11.4 per cent women.) Twenty-five cases (12 men and 13 women) showed doubtful pathologic changes (21.8 per cent men and 14.2 per cent women); and if the twenty-four cases of leucoderma are included in the list of secondary manifestations we get a total of pathologic changes in the cerebrospinal fluid in 17 per cent men and 26.6 per cent women. Of cases of tertiary syphilis exhibiting no nervous manifestations the author has only examined fifteen males and three females. In two of the males at least one of the reactions showed doubtful pathologic changes and in three others the reactions were more or less pathologic. In twelve cases all the reactions were normal; seven of these were suffereing from a syphilitic orchitis, and a second complained of a perforation of the palate. Four cases of aneurysm of the aorta were examined (three females and one male); in all these the fluid was normal. Specimens from twenty untreated patients, of whom six were males, suffering from active, late hereditary syphilis, were examined. A doubtful reaction (8 cells per cubic millimeter and Bisgaard-Ross-Jones 2-20), probably due to bleeding, was found in the case of a boy, aged nine, who showed syphilitic nodules all over the body. In two girls, suffering from juvenile dementia paralytica, all the reactions were strongly positive, and so they were in one boy aged nine, suffering from Little's disease. In three patients suffering from parenchymatous keratitis, and showing no nervous symptoms, more or less definite alterations were found in the fluids. In only three out of fifteen patients with secondary syphilis affecting the central nervous system was a quite normal cerebrospinal fluid found. Of these three cases one was suffering from atrophy of the left optic nerve, and two from a neuritis of the auditory nerve. Two other cases with an inflammation of the auditory nerves, however, showed pronounced abnormal reactions and both were examples of "nerve relapse" after treatment with salvarsan. The two patients who suffered from the sequelæ of a hemiplegia gave definite evidence of abnormalities of the cerebrospinal fluid. In two cases showing an active optic neuritis, pleocytosis was pronounced, and in two cases, combining leucoderma and slight meningeal manifestations, a positive cerebrospinal fluid Wassermann was obtained. The author has examined the cerebrospinal fluid in fifteen treated and eight untreated cases of cerebrospinal syphilis and found no differences between the treated and untreated cases. In only three cases suffering from slight cerebral symptoms, the cerebrospinal fluid was normal, or almost so; in twenty cases the proteins were increased; in seventeen the number of cells was increased and the Wassermann reaction in the cerebrospinal fluid was positive in twelve cases. The author has made observations upon eleven cases of dementia paralytica where the diagnosis was fairly certain, and upon nine more doubtful cases; in all the cerebrospinal fluid showed abnormal reactions. In all the twenty cases pleocytosis was present, but occasionally its degree was small. In all cases the Wassermann reaction in the cerebrospinal fluid was positive. All cases, with the exception of one, showed high or fairly high values with the nitric acid test as well as a comparatively high globulin fraction. The author counted the cells in nineteen cases; in eleven a pleocytosis varying from 10.3 to 123 cells per cubic millimeter was present, in five the cell count was normal and in three from 5-6.7 cells were found. In six untreated cases of tabes the Bisgaard-Ross-Jones was abnormal in five, and in thirteen previously treated cases abnormal values were found in ten. In nineteen cases the cerebrospinal fluid Wassermann was positive ten times and negative in nine cases. Judged by thirteen cases of secondary and two cases of primary syphilis, the reactions in the cerebrospinal fluid in patients showing no nervous symptoms or signs are fairly readily influenced by treatment with mercury or (and) salvarsan. In eight cases a more or less severe lymphocytosis disappeared completely, or almost completely; in three cases, in which lymphocytosis was present, the cell-count after four to six weeks' treatment remained practically unaltered, and in four cases the cell-count fell rapidly after treatment. The Bisgaard-Ross-Jones reaction before treatment was normal or almost normal in six cases, and in nine others after treatment became normal or almost normal. A slightly positive Wassermann reaction in the cerebrospinal fluid was found six times; after a single injection of neosalvarsan in all cases this reaction became negative. Thus treatment rapidly influences the reactions in the cerebrospinal fluid from cases of early syphilis.

The author's observations seem to suggest that the different reactions are somewhat more difficult to influence in tertiary than in secondary syphilis. In eight of the twelve cases of tertiary syphilis at least one of the reactions was favorably influenced and none were intensified, while the clinical symptoms generally diminished; four of the cases were somewhat inefficiently treated, and in two the reactions were little altered, and in the other two the reactions were influenced in different ways. The author treated seven cases of paresis with mercury and intravenous injections of salvarsan or neosalvarsan. In six out of seven cases the lymphocytosis diminished from a high pathologic level to a more or less normal count. In five cases the Bisgaard-Ross-Jones diminished, in two in rather an irregular fashion. The Wassermann reaction, in contrast with the cell count and the Bisgaard-Ross-Jones reaction, changed in a more irregular fashion, but for a short period in all this reaction was influenced favorably. The author examined the influence of treatment in eight cases of tabes dorsalis. The lymphocytosis diminshed gradually in three cases, was unaltered in one case, and diminished in another from 88 to 33 per c.mm. after treatment, later to relapse and yield 78 cells per c.mm. The Bisgaard-Ross-Jones gradually became less definite in five cases, but was practically unaltered in two cases. The Wassermann reaction in the cerebrospinal fluid was very variable in two cases, but on the whole tended to become more positive; in two cases the reaction was not affected by treatment and in two cases became negative.

RECOGNITION AND DIFFERENTIATION OF SYPHILITIC STIGMATA.—Ullmann. Archiv für Dermatologie und Syphilis, 1918, vol. cxxiv, No. 4.

Syphilitic stigmata in contradistinction to symptoms of disease are indelible marks from degenerative organic changes, the result of syphilitic changes and tissue lesions. In the first of the author's three illustrated cases the roseolous spots gradually passed into distinctly circumscribed atrophic and depressed cicatrices which in a way corresponded to the picture of Jadassohn's anetodermia. The second case was concerned with an eruption over the entire body, consisting of grayish-purple spots turning brownish on pressure and in part slightly papulous in character. Verrucous callosities were noted in the palms and soles. The patient had contracted the infection fourteen years previously and had been insufficiently treated. The callosities subsided upon energetic syphilitic treatment, but the eruption persisted unchanged as a stigma. The third patient who likewise presented an eruption of dark brown to slate gray spots over the entire body could not be shown to have been syphilitic and in all probability the stigmata were due to smallpox, the typical scars of which were present on the face.

SYPHILIS IN SURGERY.—Jose de Mendonça, Rio de Janiero. Brazil-Medico, 1918, vol. xxxii, p. 361.

Surgery and syphilis come in contact in at least two relationships. The first is naturally the actual intervention of surgery in syphilitic affections. The second has to do with the inhibiting or disturbing influence of syphilis upon surgery in general. The first category is rather considerable. There are numerous reasons for excising the primary lesion irrespective of the influence of this procedure on the subsequent course of the disease. In certain cases of chronic adenopathy it may be advisable to excise the affected lymph nodes. In such cases, however, as well as in similar conditions during the evolution of secondary syphilis, there are competitive procedures, such as the thermocautery for phagedena and the x-rays for chronic adenopathy. In rare cases a tracheotomy may be necessary for syphilitic laryngitis. Gummatous processes yield readily to medical measures as a rule, but cases occur in which fistulæ form and in which minor surgery is necessary. In regard to the abdominal viscera, an enlarged spleen of syphilitic nature may at times require extirpation and the recent surgical interventions for syphilis of the stomach and other viscera may be mentioned in passing. In rare cases some decompression operation for a lesion of syphilitic nature in the cranial or spinal cavities may be necessary. There are numerous other conditions of syphilitic nature which almost daily require intervention. Here belong the various forms of periostitis, the gummata which have often simulated sarcoma and certain anorectal affections. In regard to the latter the author reports in detail some seven cases. There is not much to be said of operations on luetics, for the Wassermann makes the diagnosis and enables us to cure the case in advance of operation save in emergency interventions, when treatment is in part deferred until after operation.

THE VENEREAL DISEASE PROBLEM AND THE WAR.—John H. Stokes, Rochester, Minn. The International Association of Medical Museums, Bulletin No. vii, May, 1918, p. 1.

The imperative necessity for action on the problem of venereal disease has carried Europe for the time being well ahead of this country in movements designed to deal with this problem. The Anglo-Saxon programs of England and West Australia are conservative for the trend of the times and confined to curative rather than to prophylactic effort. The programs of other European countries, under the strain of military necessity, and guided by a tradition of regulated prostitution, have adopted radical prophylactic programs in addition to the basic measures relating to treatment. Germany has progressed further than any other country in the extension of medical prophylaxis to army and civil population. Italy and France have carried officialized prostitution, following the precedent of Japan, into their army systems. In preparation for the venereal problems incident to the close of the war, Germany's preparation seems to lead the world. The United States, long backward in the movement, has now adopted a strong military with a weak or nonexistent civil program. Civil effort is still local and spasmodic in its manifestations, though encouraging. A timely combination of organized sentiment, official perspicacity and principle, and an unsavory Mexican border experience has committed us to a policy of repression of prostitution, combined with all forms of personal, educational, and social prophylaxis. The standing of the United States Army in the matter of venereal morbidity has not always been the best. We experienced the expected wave of mobilization morbidity, the National Army rate reaching the proportions of five times the present British rate. Extraordinary improvement has recently occurred. Our medical service has been only fairly efficient in the early recognition of syphilis. Educational prophylaxis by the station method, with attention to the time factor, is one of the most efficient instruments in existence for the control of venereal infection. With only average conditions, the failures range between 1 and 2 per cent of all cases treated. Social prophylaxis, based on the growing recognition of the fact that the soldier is a human being, has assumed a prominence never before attained. The familiar influences are increasing prostitution and irregular sexual relations on a large scale all over the world. The chief danger to soldiers is from professionals behind the lines, and clandestines in the war zones. Inspected prostitution seems to have no advantage over uninspected. Women are especially effective police in this field. The commanding officer is an important factor in the control of a venereal situation. This country should utilize every means to educate each man called to the colors before he is mobilized, and should at once take steps to imitate the preparations of Germany for the close of the war and the disposal of infected men, including their surveillance by civilian agencies and clinics. At these points our program is weakest. Miscellaneous points drawn from European experience include special risks to enlisted men, troop transport, convalescent infections, relation of pay to temptation, increase of syphilis in the general population, etc. There have been no strikingly new contributions to the diagnosis and treatment of venereal disease. Military necessity dominates this field also, and treatment in general has to draw a compromise between curative ideals and the refitting of the patient for further service. Standardization of treatment, a much to be desired end, has been undertaken for the United States Army. British Army results probably represent the optimum now being attained outside of Germany, on whose methods no information is obtainable.

SYPHILIS AND PARASYPHILIS OF THE CENTRAL NERVOUS SYSTEM, DIAGNOSIS, PROGNOSIS, AND TREATMENT.—M. Neustaedter, New York. Medical Record, 1919, vol. xcv, p. 265.

All methods of determining which case is beyond help and which is still amenable to treatment are purely speculative, since no positive signs are available to diagnose that *intra vitam*. Since even in cases with markedly evident organic changes, as in tabes, many symptoms have been ameliorated, notably the various crises, and in paretic and taboparetic syndromes beneficial results were obtained, we are justified in treating every case along the well-established lines.

AN EXPERIMENTAL INVESTIGATION OF THE TOXICITY OF CERTAIN ORGANIC ARSENIC COMPOUNDS.—George B. Roth, Washington. Bull. No. 113, Hygienic Laboratory, Washington, D. C., p. 61.

No marked variation in toxicity was found in either German or American salvarsan, as shown by their intravenous administration to rabbits and rats. Individual variation in susceptibility to salvarsan is quite marked in both rabbits and rats. The toxicity for rabbits and rats closely parallels the arsenic content of the salvarsan preparations examined. Neosalvarsan preparations were found to be less toxic for rabbits and rats than the salvarsan preparations examined.

CERTAIN REACTIONS FOLLOWING THE INTRAVENOUS INJECTION OF SALVARSAN AND NEOSALVARSAN, THEIR SYMPTOMS AND TREATMENT.—B. Barker Beeson, Chicago. Charlotte Medical Journal, 1918, vol. xxvvii, p. 217.

The following suggestions are of value in helping to prevent untoward symptoms after an injection: (1) The use of plain, freshly distilled water as the vehicle. It should be prepared the same day it is to be used. (2) Employ a distillation apparatus which is entirely glass. (3) The solution of salvarsan should be rendered alkaline and then a slight excess, one or two drops of 15 per cent sodium hydroxide is added. (4) The initial dose of salvarsan should not exceed 0.20 grams, of neosalvarsan 0.35 grams. As a rule one should not exceed 0.6 grams of 606, or 0.9 when giving neosalvarsan. (5) Seven to ten days should constitute the usual interval between doses. In exceptional cases they can be given four to five days apart. (6) The urine should be examined in all cases previous to the injection. (7) Be cautious in giving these drugs to alcoholics and nephritics, also to those who have cardiac lesions, or acute inflammation of the upper air passages. (8) Always give the injection on an empty stomach. Do not allow any solid food until the next day. (9) Have your patient go home at once after the injection and remain quiet for the rest of the day.

THE ARSENICAL TREATMENT OF SYPHILIS.—B. Sherwood Dunn, Paris, France. Medical Record, 1918, vol. xciv, p. 1105.

In private practice, where we can make our influence felt to a greater degree with the patient, we can pursue a course of after treatment following the indications in each case. If the Wassermann remains negative after six weeks to two months of repose, put the patient under the classical treatment by mercury, choosing by preference the soluble salts (benzoate, biniodide), giving a series of twenty injections followed by one month of repose, or ten injections per month for six consecutive months. If the Wassermann shows a tendency toward the positive when the patient presents himself after the period of repose following the first course of treatment, repeat the first course of forty days' mixed treatment and permit only three weeks to elapse before again submitting him to a serologic test. If the lumbar puncture at the end of the first treatment gives an abnormal result (hypertension, albuminuria, lymphocytosis) the arsenic treatment alone or mixed with mercury should be given until these evidences return to normal and then the mixed or mercurial treatment should be inaugurated, but with not more than one month of repose between each cure. If the severe accidents appear (cephalalgia, cerebral obtrusion, vertigo, fever, nervous phenomenon), it is better to follow the lighter treatment by small dosage (0.05 to 0.15 of luargol in particular), repeating until these symptoms are brought under control. After the patient has been brought to normal (Wassermann and lumbar negative), we still persist in following the classical treatment with mercury over a period of five years, making a Wassermann test at regular intervals to insure perfect control. Even with every known remedy and every precaution taken, we can not be certain of a complete and permanent cure, and the author does not believe we will arrive at a certainty of cure for this malady, which has been the curse of the human race since the dawn of history, until we have brought it under the influence of that magic cure for all diseases of microbic origin, serum therapy, if we ever arrive at a degree of knowledge that permits it.

ATROPIN AND INDUCED ANTIANAPHYLAXIS.—J. H. Stokes, Rochester, Minn. Journal of the American Medical Association, 1919, vol. lxxi, p. 241.

The acute "nitritoid" crisis or reaction to arsphenamine is a form of anaphylactic shock, explainable on physicochemical grounds as the result of a precipitation either of the drug from its colloidal solution, or of the colloids of the blood plasma, by the drug, or by an impurity. The reaction following the injection of an acid or only partially alkalinized solution of arsphenamine either too rapidly or in too high concentration is presumably of the same type. The nitritoid crisis can apparently be inhibited by a previous injection of atropin ($\frac{1}{50}$ grain), which further suggests that the reaction is a form of anaphylactic shock. The induction of antianaphylaxis as described further supports the belief that the nitritoid crisis is a form of anaphylactic shock. The induction of antianaphylaxis in patients exhibiting persistent idiosyncrasy to arsphenamine or neoarsphenamine has proved clinically useful, and, as a means of increasing their tolerance of the drug, deserves further trial and study.

NOTES ON THE DECOMPOSITION OF ARSPHENAMINE.—John B. Rieger, Boston, Mass. Journal of Laboratory and Clinical Medicine, 1919, vol. iv, p. 181.

Commercial arsphenamine may contain an arseniureted methyl compound, which decomposes either in the ampule or in solution, with liberation of arsenous oxide or a cacodyl-like substance. Some preparations betray the presence of the arsine by their garlic-like odor when dissolved; others develop it only after having stood in solution for hours. According to the amount that may have accumulated, the dosage and the idiosyncrasy of the patient, a reaction marked by fall in blood pressure, dyspnea, and cyanosis may occur. Once the drug has been injected, the occurrence of subacute or chronic arsenic poisoning is determined by the margin that exists or may be made to exist between its elimination and its reduction by the tissues. There is evidence that this reduction to metallic arsenic occurs too readily for safety with present commercial preparations of arsphenamine.

SYPHILIS AND SALVARSAN.—Villapadierna, Madrid. El Siglo Médico, 1918, vol. lxv, p. 1033.

The author, who is one of the staff of the well-known hospital for urology and venereal diseases, the San Juan de Dios, refers to the large material which is subjected to salvarsan injections and wishes to give an opinion which is purely personal in character on the employment of this resource. In his institution the intravenous method is the exclusive one in use. Neosalvarsan is now used in place of 606, with an elaborate technic and apparatus. The usual dose is 60 to 75 cgm. with 90 as a maximum. The amount of liquid used is reduced to the minimum for solution of the drug. Properly given the reactions are minimal. In primary syphilis the results are of the best and the smaller chancres vanish after a single injection. On the other hand the large and infiltrated primary sore requires a number of injections. The special forte of salvarsan in contrast to mercury lies in the direction of producing prompt and thorough cicatrization. Contrary to the general verdict the author extols salvarsan in secondary syphilis: here the way in which the drug clears up these cases is marvelous, and this is particularly to be noted in prostitutes in whom the rapid recession of secondary symptoms must facilitate the resumption of their calling. The author is no less enthusiastic about ordinary tertiary syphilis and even in the so-called malignant type he has seen four remarkable cures. His eulogy extends throughout the entire domain of the disease, but he believes that a course of mercurialization is often advantageous for the result due from salvarsan. Only in the metasyphilitic affections are the results ephemeral and the treatment inefficacious. Along with treatment the author emphasizes methods for precocious recognition of the spirochete and recently the silver salts have been used for staining the field preparatory to the use of the ultramicroscope.

Clinical and Physiological Studies of the Rectal Absorption of Novarsenobenzol.—Azemar, Toulouse. Annales de Dermatologie et de Syphiligraphie, 1918, vol. vii, p. 14.

Arsenic by the rectal route has been used since 1912, or ever since Bogrow, a Russian, administered it in a cocoa butter suppository. Others soon followed with suppositories and enemata. An injection technic was devised at an early period, but on the whole the results were not encouraging. A few like Rajat were enthusiastic and the latter reported good results in a series of 125 cases. A field seemed open here for the intensive use of salvarsan, for in addition to the usual routes the drug could also be thrown into the rectum. From another angle an opportunity was given for a competitive trial of the intramuscular, intravenous and all other routes for exhibition. In one such a trial the intrarectal route appeared to be superior (Weill, Morel and Mouriquand). As early as 1913, Brochard had obtained good results in the treatment of yaws by the intrarectal route. The merits of rectal arsenotherapy were also extolled in other spirilloses. Whatever the merits or demerits of organic arsenic in rectal therapy, the fact remained that neosalvarsan seemed especially suitable to this form of exhibition, at least from the theoretic viewpoint. Two Chicago men were the first to report favorably on the new medicament when given by the rectal route. In the following year Benoit went extensively into the subject of the intrarectal treatment of syphilis by neosalvarsan. He concluded that it was inferior on its face to the intravenous method, but that there were compensations which went far to compensate for the drawbacks, provided the dosage was large. These compensations were expressed as simplicity in technic and absence of danger. The remainder of the article is devoted to the description of an elaborate technic and of 36 case histories intended to illustrate the excellence and sufficiency of the resource in the treatment of syphilis. In any effort of this sort it is necessary to consider all of the aspects of the question, such as the fate of the arsenic exhibited; and this is duly dealt with. The author concludes that an aqueous solution of neosalvarsan is rapidly absorbed and that in the second hour it is present in the urine in ponderable amount. This amount increases up to a certain period and is usually absent from the urine by the sixth day.

ARSPHENAMINE AND NEOARSPHENAMINE.—Vasconselos, Mexico City. Revista Medica, 1918, vol. i, p. 101.

The author begins with a consideration of the commercial equivalents of German-made salvarsan and neosalvarsan. Among these he is interested especially in arsphenamine and neoarsphenamine so-called, names proposed or rather endorsed by a Federal Commercial Commission of the United States. Upon the labels of ''American-made Salvarsan'' one finds in inconspicuous type the word ''arsphenamine,'' and this is also true of the original German salvarsan and some of its commercial equivalents in other countries. Concurrently the labels of novarsenobenzol, neodiarsenol and neosalvarsan bear the mark ''neoarsphenamine.'' Numerous other well-known advertised commercial substitutes do not come under the head of arsphenamine and the author does not consider them. When neoarsphenamine was introduced as neosalvarsan in 1912 the author was favorably impressed with its claims, but when a comparison was made in the clinic the author was not convinced and after some years (1917) returned to the use of the old remedy, because, as a rule, it is not only more prompt and efficacious in its action, but is actually better tolerated. Since the neosalvarsans in the market have of late been in part spurious, the author now uses arsphenamine exclusively under whatever trade name it bears. The neoarsphenamines still have their special indications. Other syphilographers come to various conclusions by no means in close accord and some prefer the newer salts as routine remedies. Socalled salvarsan-sodium has its friends, while some practitioners see no superiority of one over another remedy. Several syphilographers of note take exactly the author's view.

ADMINISTRATION AND ABSORPTION OF NOVARSENOBENZOL BY THE RECTUM.—Azemar. Annales de Dermatologie et de Syphiligraphie, 1918-19, vol. vii, p. 14.

The author reaches the following conclusions from the results of his physiologic and clinical study: Novarsenobenzol injected in watery solution into the rectum is rapidly absorbed, so that during the second hour following, ponderable amounts of arsenic may be recovered from the urine. The quantity of urinary arsenic increases until the third day after the enema and then disappears entirely in the majority of cases by the sixth day. Compared with intravenous injection, elimination is slower and less in mass but eventually more absolute,, because in intravenous exhibition traces may be found in the urine as late as the fifteenth day. The rectal treatment of syphilis by novarsenobenzol is relatively efficient, easy and simple in execution. It is a medical resource which has few or no contraindications. On the other hand its therapeutic effects are less prompt, less thorough, less constant and less permanent than those of the intravenous exhibition. The intrarectal method is well suited to the latent stage of syphilis and as a prophylactic but it is not indicated in combating active clinical manifestations. For the latter the intravenous method is always indicated. The rectal method is also excellent when we wish to combine mercury with arsenicals in an inunction course or a course of intramuscular injections. The dose per rectum for healthy adults should be large—0.9 gm. Small and repeated doses do not yield the same results. The intervals should be at most six days, and about five injections usually suffice for complete cure. The author to date has seen not the slightest untoward result, whether immediate or remote, from the use of the intrarectal method.

THE ADMINISTRATION OF NOVARSENOBENZOL PER RECTUM.—Leo E. Grajewski, Detroit, Mich. Urologic and Cutaneous Review, 1919, vol. xxiii, p. 22.

Properly handled, the rectal administration of novarsenobenzol can be regarded as taking the place in all cases of other procedures, especially intravenous injection. But apart from this it has special indications. For instance, we can have recourse to this procedure whenever for any reason intravenous injection presents a difficulty of some kind, when the veins are not prominent in spite of the application of a constricting hand above the elbow or when they are separated from the skin by a thick layer of adipose tissue, when the veins are very small and especially this mode of administration is suited for children. The dose administered for healthy adults was usually 0.9 gm., for children 0.6 gm., repeated at intervals of six days with six injections, which completed the cure; on the other hand, if still positive, the course of treatment was repeated and combined with mercury.

THE SPLENIC REFLEXES OF ABRAMS IN THE TREATMENT OF SYPHILIS. —Albert Abrams, San Francisco. Medical Record, 1919, vol. xcv, p. 96.

From an investigation of a comparatively large number of cases of syphilis, coupled with observations bearing on the results of treatment, the author deduces the following: The usual depositories for the luetic virus are the spleen and liver, notably the former. When the splenic and liver reflexes of contraction are evoked by concussion of the second lumbar spine there is an immediate extrusion of the virus into the circulation. The spleen is not a quiescent viscus, but undergoes periodic changes in volume. Emotions, digestive disturbances, and other factors may precipitate extraordinary volume changes in the spleen, thus eliminating the products of the disease into the circulation, causing an exacerbation of symptoms present or producing them if absent. In parasyphilitic diseases the parasites are found in the "dead corners" of the organism, and resist the action of drugs. Similarly, virus lodged in the spleen is equally resistant. Elicitation of the splenic reflex is therefore a valuable adjunct in syphilotherapy. The same fact applies in all cogency to other infections and in a number of diseases, notably "fatigue neurasthenia."

TREATMENT OF ANTENATAL AND POSTNATAL SYPHILIS.—John Adams, British Medical Journal, 1918, p. 541.

Syphilitic pregnant women can be treated with salvarsan, even up to the day of their confinement, with safety and every advantage. A mother whose blood gives a positive Wassermann reaction may, after treatment, be delivered of a child whose blood gives a negative reaction. The child may continue to thrive and give a negative blood test. Syphilitic children can safely be treated by salvarsan immediately after birth. Salvarsan, combined with treatment by mercury has a more certain and quicker action in producing a negative Wassermann reaction in the child than in the mother. In nearly all syphilitic children born alive, treatment can convert a positive Wassermann reaction into a negative, and such children appear to become healthy and show regular weekly gain in weight.

DEFORMITIES OF THE NOSE RESULTING FROM SYPHILIS: HOW SHALL WE TREAT THEM?—William Wesley Carter, New York. Medical Record, 1919, vol. xcv, p. 318.

Bone transplantation in syphilitic subjects is distinctly contraindicated. While all bones in the body do not show grossly the same vulnerability to syphilitic invasion as the nasal bones, the septum, the bones of the skull, etc., yet we must remember that this vulnerability is strictly a local manifestation of minor resistance to the specific virus, which permeates all of the bones of the body alike. In closing a gap in the ala nasi the author has, on more than one occasion, had the raw approximated surfaces fall apart at the end of a week, showing that they possessed no more vitality or reparative energy than two pieces of leather. The preliminary treatment, therefore, of syphilitic deformities resolves itself into the problem of eliminating, or at least getting under control, the specific disease and overcoming the nutritional derangements from which all of these patients suffer to a greater or lesser extent. So far as bone transplantation is concerned, it is useless to attempt it when the metabolic balance is badly disturbed and the patient's nutrition is far below normal.

FURTHER NOTES ON MARGOSIC ACID AND ITS SALTS AND OBSERVATIONS ON THEIR CLINICAL USE.—Karuna K. Chatterji, Calcutta, Indian Medical Journal, 1918, vol. liii, No. 10, p. 377.

In margosic acid and its salts the medical profession will find a powerful therapeutic agent which can be used in combating infections of diverse nature. The author has tried to ascertain its specific action in syphilis. In the cases reported it will be seen that the manifestations of the disease have cleared up rapidly. Regarding Wassermann reaction, it has been rendered negative in one case and it has remained so after a dose of provocative injection of galyl. In three other cases the Wassermann reaction has been considerably reduced. The effect seems to be more pronounced in tertiary lesions. This may be due to the fact that the margosates act best when there is a mixed infection of the spirochetes with some pyogenic organisms.

THE TREATMENT OF GENERAL PARESIS.—Clarence A. Neymann, and Nathaniel H. Brush, Baltimore. Archives of Internal Medicine, 1918, vol. xxii, p. 245.

Twenty-four cases of general paresis, treated according to the author's method, alternately once a week with arsphenamine serum and mercurialized serum are described. Six patients were so markedly improved that five of them were able to resume their occupations. All of them gave practically negative serologic findings. The average duration of the present status is fifteen months. They consider these are arrested cases. Six others were somewhat improved, four resuming their occupations, while two are continuing their treatment. All of these were somewhat improved serologically. Six showed no clinical or serologic improvement, except in one case. This is undoubtedly a clinical remission; the serologic status remained unchanged. The last six were harmed by the treatment. One developed a paraplegia; two became incontinent; one died of acute arsenical poisoning and one developed an arsenic neuritis; finally, one died in convulsions, possibly as the result of the treatment. Whenever the serologic findings tend to become negative, they usually change in the following order and manner: The cell count is first reduced to normal. The Wassermann reaction then becomes negative. The paretic colloidal gold curve changes to an atypical or negative one. The globulin tests become less marked, but traces of globulin usually remain. Twenty-three per cent of all the paretic patients examined in this clinic show negative blood Wassermann reactions.

Paresis—A Look-Back on Recent Therapy.—Jas. K. Hall, Richmond, Va. Virginia Medical Monthly, 1918, vol. xlv, p. 157.

Any kind of treatment of paresis whatsoever is, in the author's opinion, inadequate and unsatisfactory. Although we now know the specific cause, and understand fairly well the course of the malady, we are unable to produce cures, notwithstanding the fact that we are provided with two or three so-called specifics. What are the causes of our gloomy view of paresis? The disease is, in the first place the result of long-standing infection of the central nervous system—the most important but the most easily injured portion of the body. Even when the diagnosis of paresis is made early, irreparable damage has already been done. The parasiticides at our disposal are probably not altogether adequate, and they are certainly not harmless. If given in strength sufficient to kill the parasite, they are prone to kill the patient, or to add to the damage already wrought by the disease.

Intraspinous Therapy in Urology and Syphilis.—H. W. Howard, Portland, Oregon. Northwest Medicine, 1919, vol. xviii, p. 19.

One-half hour after the administration of .6 gm. of arsenobenzol, 50 c.c. of blood are taken in a dry syringe. As much of this as can be contained is placed in four dry sterile centrifuge tubes. In due time the clot which has been allowed to form is carefully separated from the walls of the tubes. The tubes are now centrifuged at moderate speed for about twenty minutes and then let stand for an additional ten minutes. The serum will have completely separated from the clot and should now be pipetted off into a graduated test tube, containing the desired amount of bichloride of mercury in solution. The blood will yield in all about 18 c.c. of serum. The tube is corked and placed in a water bath at 55° C. for 30 minutes to inactivate, which completes the preparation of the serum. The intraspinous operation is done in a hospital. Having received previously one-fourth grain of morphine hypodermically, the patient is placed upon his side with the body extremely flexed. Iodine having been liberally applied, the first interspace above or below the level of the iliac crests is chosen for the puncture. A small sharp intraspinal needle is introduced until cerebrospinal fluid returns. Approximately as much of this is withdrawn as the amount of the treated serum to be introduced. The serum is now allowed to flow in from a graduated burette connected to the needle by eight inches of rubber tubing. It should flow in slowly; this tends to minimize reaction. The last of the serum which will stand in the rubber tubing on account of intrathecal pressure is forced in by superimposing the spinal fluid which has been withdrawn. The patient is placed in bed without a pillow, the foot being elevated about a foot for a few hours. Morphine is to be given, if requested, which is not the rule.

Some Observations in Neurosyphilis.—John R. Thrasher, Indianapolis. Mississippi Valley Medical Journal, 1919, vol. xxvi, p. 46.

Salvarsanized serum is a most useful aid in combating neurosyphilis. The biggest factor in the successful handling of neurosyphilis is early diagnosis and early treatment. Paresis would be a rarity provided the diagnosis of the invasion of the central nervous system were made early and promptly. The majority of the invasions of the central nervous system occur just prior to, or early in, the secondary stage of syphilis. Spinal puncture, with complete examination of the spinal fluid, should be made as early as possible in every case of syphilis. Cases dismissed as cured should be kept under observation and examination for years.

Pseudoreinfection, Superinfection and Reinfection in Syphilis. —Rùhl, Turin. Pathologica, 1918, vol. x, p. 173.

The subject of pseudoreinfection is bound up in part in that of successive chancres, in one type of which the presence of one chancre is responsible for one or more others by autoinoculation. In another type of successive chancre there has been exposure to different sources of contagion at different times. In both types the consecutive lesion can develop only within a certain interval before the entire body, or at least the entire integument has become immune to inoculation. Quite a different type of pseudoreinfection is seen in chancre redux and other forms of so-called reinduration. In chancre redux proper, the relapse occurs in the site of the original chancre, but there are forms of pseudochancre which occur at a distance from the latter, either slight or more or less remote. A number of quite different lesions are comprised under this type such as indurated mucous papules and chancriform gummata. Certain nonsyphilitic lesions in a syphilitic may also indurate. Superinfection is largely associated with experimentation, otherwise it presents in part conditions similar to those seen in successive chancres. Those who have contracted a chancre can be subjected to autoinoculation without prejudice and both the primary and secondary incubation periods have been freely tested in this respect. In the clinic the subject coincides with one phase of multiple successive chancre in which there has been exposure to two consecutive sources of contagion which can be definitely fixed. Another type of superinfection is encountered later in the disease when there are clinical evidences that old syphilis still persists. This class of cases belongs in close touch with true reinfection, the two subjects overlapping. The subject of superinfection in syphilis has done much to upset our notions of immunity and its possibility has naturally been subjected to severe criticism just as in like manner the existence of reinfection has been disputed. The skeptics see in both phenomena only a reawakening of old syphilis or else deny that syphilis ever existed. The existence of both phenomena, however, has been firmly established.

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Original Articles

INTRASPINAL THERAPY IN NEUROSYPHILIS

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MODERN diagnostic methods and modern treatment controlled by the Wassermann reaction in the blood and spinal fluid, together with other standardized spinal fluid tests, have made the study and treatment of syphilis the most absorbing and fascinating subject in medicine. Exact knowledge has largely replaced vague clinical impressions so that we are able to prognosticate the future of a patient affected with the disease with more certainty than in any of the other chronic infections. New facts are being slowly acquired as to the behavior of the spirochetes when they enter the blood and lymph streams, their sites of predilection and the tissue responses which they call forth. Many of the older views as to the late implication of the nervous system, the cardiovascular apparatus, and the viscera are in many respects erroneous, as they are based entirely on the end results of the infection and disregard the pathologic processes during the long period of so-called latency. Knowledge acquired by clinical study, serology, and autopsy findings leads to the belief that foci are established in the various tissues which may require years to modify or destroy functional capacity.

The majority of patients with syphilis receive treatment with more or less regularity and intensity. A complete cure is the exception rather than the rule unless treatment is begun in the early months of the infection. The progress of the disease is delayed or held in check for months or years, but is frequently subject to relapses and slowly progressive tissue degeneration. An aortitis or aortic insufficiency is not the result of a sudden invasion of the aortic walls or valves by spirochetes many years after the primary sore, but the effect of a slow tissue reaction due to the implantation of the organisms in the florid stage of the disease, manifested first by a lymphocytic and plasma cell infiltration about the small vessels of the adventitia and media followed by a replacement fibrosis and disturbance of function. When, therefore, an aortitis is diagnosed it has probably been in existence for years and finally reveals itself by gross clinical signs attended by more or less functional impairment.

The pathologic studies of Warthin in visceral syphilis which show that spirochetes may be harbored for years with slight or no reactive phenomena support the theory of the persistence of the infectious agent *in loco*. Additional arguments in favor of this hypothesis are also afforded by the reappearance of late lesions in the skin or mucous membranes at or near the site of early ones, and the recurrence of keratitis in congenital lues. It does not require a great tax on our reason to suppose that the spirochetes behave much the same way in all the organs which they invade. We may, therefore, transfer our argument to the central nervous system. With its more specialized centers and tracts spirochetal attacks may cause marked subjective or objective symptoms and signs like headache, delirium or paralyses of the most varied types. On the other hand an individual so infected may remain free from all symptoms for years until some important center or tract is compromised. The case histories of some of these patients afford a most interesting narration of family tragedies, business or professional failures, of eccentricities of behavior which have worried and puzzled their friends and families until an eye examination has revealed pupillary changes or some localizing lesion has indicated the necessity of a careful physical and serologic examination. In some of these cases, however, where slight character defects are the only deviation from the normal life, the objective signs may be practically nil while the blood and spinal fluid reveal the formula which speaks for paresis.

"Paresis sine parese," as Southard and Solomon well put it, may exist for years without the well-known stigmata which indicate advanced degeneration. It is not, in my opinion, an invasion of the brain from five to twenty years after the primary sore which suddenly appears with speech disturbances and grandiose ideas leading to the patient's death in from two to three years. The spirochetes are deposited in the cerebral cortex during the period of generalization of the organisms, as in aortitis and visceral syphilis, where they may remain without reactive phenomena, or spirochetes hidden away in the deeper parts of the brain may act in the same way as in the other organs. Few lesions may be present and only after years produce a disturbance of function. In certain cases they may temporarily stimulate the intellectual powers and lead to achievements of more than normal brilliancy. Paresis is, therefore, comparable to aortitis in an early implantation of the organism of syphilis, the slowly progressive course of the pathologic changes leading to obliteration of the lumen of the smaller vessels, and finally to atrophy of the essential brain cells. As in other organs the progress of the infection in the central nervous system is modified or delayed by therapeutic agents given by the usual channels. It is seldom cured; the modified or delayed infection is latent for a time and then relapses. This condition may continue for years before it finally terminates in irreparable damage. The appearance of some characteristic symptoms of cord syphilis or mental changes so gradual in their onset as scarcely to be noticed may lead to the diagnosis of neurosyphilis. The patient is then said to have developed tabes or paresis five, ten, or twenty years after the primary infection.

If we admit, as I think we must, that neurosyphilis, like its prototype in other organs, may have long periods of latency, it is not difficult to believe that the spirochetes gained entrance to the nervous system in the period of their greatest dissemination, i.e., the florid stage. Since attention has been directed to early neurosyphilis, careful clinical examination has uncovered a much larger number of cases. More definite knowledge has been acquired by spinal fluid examination at this time. It has been shown by numerous observers that from 25 per cent to 35 per cent of patients in the first year of the infection show pathologic changes in the spinal fluid. In some of these patients after minor damage to the meninges, tracts, or cells the infection may spontaneously disappear or be cured by treatment. This statement is confirmed by the observation of cases of abortive tabes with pupillary changes and slightly altered or absent deep reflexes, with negative blood and spinal fluid findings. In our routine examinations of neurosyphilitics we have records of a number who have remained stationary for years and have presented a negative serology after repeated investigations. The more usual course is the establishment of foci in the cerebrospinal axis which progress with varying degrees of rapidity and eventually lead to one or the other well-known types of neurosyphilis.

Assuming that the foregoing statement as to the early implication of the viscera, cardiovascular and nervous systems is correct, the vast importance to the individual of the early recognition of such an involvement is self-evident. We have, fortunately, in the Wassermann test an indication of the continued presence or activity of the causative factor in some part of the body and as long as the test continues positive the future of the patient is menaced. An endeavor should always be made to detect the organ or organs which may harbor the spirochete. Statistics show that a larger percentage of deaths is due to cardiovascular disease of syphilitic origin than to any other phase of the disease. For this reason a persistent positive serum reaction should lead to a careful examination of the heart and aorta. Small visceral lesions may persist for years in organs not accessible to physical examination. Syphilis, of course, does not limit its activity to one system or organ. The most obtrusive symptoms may overshadow the others and lead us to forget that we are dealing with a general and not a purely local condition. A positive Wassermann reaction which remains for years uninfluenced by intensive treatment or which returns after treatment is discontinued is not infrequently caused by neurosyphilis without any or very few objective signs. The blood reaction becomes negative for a time after treatment, but is again reinfected by the spinal fluid. This observation deserves more general recognition. I have again and again observed patients over a period of years who have consulted one physician after another in their efforts to bring about a permanent reversal in the blood. Well-directed inquiries may elicit the admission of a failure in sexual power, loss of ambition or defect in memory; the reflexes may be hyperactive and unequal and the pupils sluggish to the light reflex. In such cases a fluid examination reveals the source of the refractory Wassermann reaction.

The systematic employment of intraspinal treatment in a large number of cases during the past five years in which the results have been carefully controlled by repeated examinations of the spinal fluid has enabled me to draw rather definite conclusions as to the type of cases we may hope to cure or benefit by its use. By the employment of a proper technic largely developed as a result of a wide experience unfortunate mishaps can be prevented and the full value of the injections realized. A serum properly prepared and diluted with from 30 to 40 c.c. of spinal fluid before introduction into the spinal canal may be employed without danger in the vast majority of patients in whom indications are present for its use.

The method which I have found of greatest value is as follows: The patient is given an intravenous injection of salvarsan and approximately one-half hour later 50 c.c. of blood are withdrawn from an arm vein. This is permitted to clot overnight in the refrigerator. The next morning it is centrifugalized and the serum pipetted into a sterile tube. After a second centrifugalization to insure removal of all red blood cells, the clear serum is pipetted into another tube. To this is added the desired amount of salvarsan; namely, from $\frac{1}{10}$ to $\frac{1}{4}$, $\frac{1}{3}$ or in certain cases of paresis $\frac{1}{2}$ mg. This mixture is then inactivated at 55° to 57° C. for one-half hour. To arrive at the proper dosage for intraspinal therapy we make a dilution of salvarsan of which 30 c.c. represents 0.1 gm. of the drug; 10 c.c. is then further diluted with 0.5 per cent saline solution to 35 c.c., of which 1 c.c. equals 1 mg. of salvarsan. In the administration of the medicated serum a lumbar puncture is made and about 10 to 20 c.c. of fluid withdrawn. A small gravity tube with a capacity of about 40 c.c. is attached to the needle and the fluid allowed to flow in until it holds about 30 c.c. To this is slowly added the serum and the mixture permitted to flow back into the canal.

In order to make my position quite clear regarding the indications for intraspinal therapy, I desire to emphasize the statement often made that the method in question is of value in certain types of neurosyphilis which fail to respond to treatment by other channels and in which the spinal fluid reveals an active syphilitic lesion. If a patient, after intensive treatment with salvarsan, mercury, and potassium iodide, shows little or no improvement in his symptoms, blood or fluid reactions, some other method of therapeutic attack would clearly be indicated. Rapid and decided clinical and serologic improvement following the introduction of a new factor, even though the original procedure might be continued, would strongly suggest to a mind free from prejudice that the new factor was responsible for the change in question. The preparation of a proper serum necessitates a preliminary intravenous injection so that it would be difficult or impossible to comply with the criterion established by our critics and use the intraspinal therapy uncomplicated with other procedures. Intensive intravenous salvarsan injections are not infrequently followed by jaundice, dermatitis or other symptoms of arsenic poisoning, making it necessary for these patients to receive their serum from another treated case.

Our data regarding the value of intraspinal injections alone are not sufficient to enable us to draw any definite conclusions, but this much we have learned, that, in a number of cases where intravenous treatment had to be intermitted on account of reactions and sensitization to the drug, the spinal fluid became entirely negative from the use of subdural injections only, the blood in several of these patients still remaining strongly positive. In these cases, too, there was a concomitant improvement in the clinical picture.

Invasion of the central nervous system occurs, as I have shown, during the florid stage of syphilis and often manifests itself in spite of intensive treatment with salvarsan and mercury, as exemplified in cases 1, 2, and 3. This early meningitis or meningoencephalitis continues to progress until the new factor intraspinal therapy is introduced. It then declines with great rapidity. Will our unprejudiced critics accept such evidence? The arguments employed against salvarsanized serum in neurosyphilitics would apply with equal force to the use of antimeningitis serum in cerebrospinal meningitis. The latter serum is only effective, however, when introduced into the spinal canal.

I have demonstrated again and again in my laboratory the persistence of positive phases in the spinal fluid in patients treated in the most intensive manner by the orthodox methods over long periods with little or no change except in the cell count and slight clinical improvement. Intraspinal therapy has been followed by persistent negative phases and clinical improvement or cure. I am, therefore, becoming more and more convinced of its value, and believe the failure of others to obtain like results to be largely dependent on imperfect technic and early discouragement because of slow results.

Since adding salvarsanized serum to 30 or 40 c.c. of withdrawn fluid and permitting the mixture to slowly return by gravity, the results have been more rapid and striking. In this manner a larger quantity of spinal fluid is medicated and possibly a positive pressure established. In 75 cases of various types of neurosyphilis all the findings are negative, many of them persistently so for periods of one to three years.

Activation of latent foci or lesions in the central nervous system may follow the administration of mercury or salvarsan and cause an acute encephalitis and death. These so-called Herxheimer reactions though presenting grave symptoms as a rule gradually subside and are frequently followed by decided clinical improvement. It is not always possible to foresee them, but they can usually be prevented by careful preliminary use of mercury and salvarsan in moderate doses before the use of salvarsanized serum intraspinally.

The introduction of salvarsanized serum into the spinal fluid of a patient with a lesion or lesions of the posterior roots is often followed in the early period of the treatment by severe root pains. After the second injection the reaction is less severe and finally disappears. At times some of the phases in the fluid become more intense, such as an increase in the globulin and a rise in the cell count. The tabetic pains and other symptoms which existed before the injections, disappear or are markedly modified and generally in proportion to the intensity of the reaction. Similar reactions have appeared after intravenous treatment, but are usually less pronounced and followed by less improvement in the lightning pains. They have also been noted in cerebrospinal meningitis and in focal brain lesions.

Syphilitic patients in every stage from the appearance of the primary sore to the development of well-marked tabes or paresis come under my observation. As a systematic examination of all these cases is made, including the spinal fluid, a larger percentage of patients in the preparetic or pretabetic stage are seen. Careful neurologic examination may show pupillary changes or alteration in the reflexes or other evidence of involvement of the neuraxis, but some are without somatic signs. A larger number are met with showing serologic evidence of syphilis in the absence of objective signs than patients with positive signs of syphilis showing negative fluid reactions. Because of the character of my work these cases are detected earlier than those which consult the neurologist and are for that reason more amenable to treatment.

Table I

Correlation of Serology with Clinical Neurosyphilis from an Examination of 5000 Cerebrospinal Fluids

		CEREBROSPINAL FLUID			
	SERUM	CELLS PER C.MM.	GLOBULIN	WASSERMANN	GOLD SOL
TABES					
a. Progressive	Positive in 70%	30-350 or more	Strongly positive	Positive in high dilutions	Luetic curve
b. Stationary		0-25	Positive or negative	Negative or positive in low dilutions	Negative or luetic curve
PARESIS	Positive in 98%-99%	25-350 or more	Strongly positive	Strongly positive in high dilutions	Paretic curve
CEREBROSPINAL SYPHILIS					
Meningitis	Usually Positive	as high as 2000 or more	Strongly positive	Usually positive in high dilutions	Luetic or paretic curve rapidly changed to luetic curve by treatment
Meningo-encephalitis Meningo-myelitis	Usually positive	Slight or great excess	Usually strongly positive	Usually positive in high dilutions	Luetic or paretic curve rapidly changed to luetic curve by treatment
Arteritis or endarteritis	Positive or negative	none or normal	Positive or negative	Usually negative	Negative or luetic curve
Meningo-arteritis	Positive or negative	none or excess	Positive or negative	Positive or negative	Negative or luetic curve
Gumma	Positive or negative	none or excess	Positive or negative	Negative or positive in low dilutions	Luetic curve or negative

A proper grasp of the treatment of neurosyphilis in its multiform manifestations can only be acquired by a prolonged study of the serology of the spinal fluid as correlated with the clinical symptoms.

Indications for and the control of treatment are more accurately afforded by the findings in the fluid than by any other method at our command. The activity of spirochetes in the central nervous system is reflected, with rare exceptions, in the fluid, so that we are able to obtain with a fair degree of accuracy indications which favor or oppose this treatment, due regard being taken for the clinical signs or symptoms.

The serology of the more usual types of neurosyphilis is shown in Table I based on a study of five thousand spinal fluids.

A pure type of arterial syphilis of the brain or cord with a negative serology, or with only an excess of globulin and a low cell count, affords no indications for intraspinal therapy. In this condition dependence must be placed solely on antisyphilitic drugs given by the usual channels. The advocates of the intraspinal method have always insisted on the presence of definite serologic and clinical indications for its employment and have favored in the majority of cases the preliminary use of drugs in the ordinary way. In rapidly developing optic atrophy or in other cases where long experience has shown the futility of intravenous therapy the method should not be too long delayed. Many of the patients who consult me for neurosyphilis have been treated intensively by all the available methods without affecting the clinical symptoms or the serology. In such patients it would be a waste of time to repeat a procedure which has failed.

An early syphilitic meningitis with a high cell count with other positive phases offers the most favorable prognosis. The sooner the meningitis is detected and treated, the more rapid the response to treatment and the less the danger of involving the underlying brain tissue. As these cases often develop during active treatment with salvarsan intravenously combined with mercury, and progress in spite of such treatment, further use of the methods in question is insufficient and is apt to be followed by disaster.

The accompanying charts (cases 1, 2, and 3) show the rapid results which followed intraspinal therapy.

Case 1. Syphilitic Meningitis

L., physician, age 32. Initial lesion of thumb in November, 1916, followed by secondaries. Treatment begun with appearance of latter. Two months later right-sided parietal headaches. Lumbar puncture made in May, 1917, was said to show 104 cells with the other findings weakly positive. After three intraspinal injections the fluid was said to be normal. Headaches did not entirely disappear and became more intense a few months later. He suffered from insomnia, great depression and impairment of mental processes. He lost 24 pounds in weight.

Was first seen November 20, 1917, when he complained of severe headache, nervousness and insomnia. On November 26 he became very excitable and developed a delirium lasting several days.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
11/28/17	416	3+	4+ 0.4 c.c.	1123321000	11/28/17 —
12/ 8/17	43	+	4+ 0.6 c.c.	1123221000	2/ 9/18 —
12/22/17	11	+	3+ 0.8 c.c.		3/25/19 —
1/ 5/18	7	±	4+ 1.5 c.c.		
1/19/18	2	±	— 2.0 c.c.	0000000000	
1/30/18	0	±	— 2.0 c.c.		
2/ 9/18	1	—	— 2.0 c.c.	0000000000	
3/29/19	2	—	— 2.0 c.c.	0000000000	

Treatment from November 23, 1917, to February 9, 1918:
8 intravenous injections salvarsan.
7 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/5 to 1/4 mg.).

Results: After three intravenous and two intraspinal injections the patient's mental condition entirely cleared and his headaches disappeared. A report received from him recently states that he feels unusually well mentally and physically and is able to look after a large practice without inconvenience. He has no insomnia and has returned to his normal weight.

CASE 2. SYPHILITIC MENINGITIS

S., age 45. Chancre in April, 1916. No cutaneous secondaries. Wassermann 4+. Treatment from April, 1916, to August, 1916: 7 intravenous injections of salvarsan and 16 injections of mercury. Owing to absence from city treatment was intermitted.

Early in October, 1916, patient became nervous and restless, had mild generalized headaches and nausea. For several days he had transient attacks of aphasia and numbness of right arm. Returned to New York October 28; examination revealed weakness right side of face, very active deep reflexes, greater on right side; pupillary outlines slightly irregular, light reflexes prompt.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
10/31/16	944	4+	4+ 0.2 c.c.	5555542100	5/ 6/16 ++++
11/24/16	90	4+	4+ 0.4 c.c.	4444430000	6/14/16 ++
12/ 6/16	31	3+	4+ 0.6 c.c.		8/12/16 —
12/16/16	30	2+	4+ 0.8 c.c.		10/31/16 ++++
12/30/16	30	3+	4+ 1.0 c.c.	1133320000	3/ 3/17 —
1/12/17	50	2+	4+ 1.0 c.c.	1123310000	9/ 6/17 —
1/27/17	28	2+	4+ 1.0 c.c.	1123210000	1/12/18 —
2/10/17	20	+	4+ 1.0 c.c.		
3/ 3/17	21	±	± 1.0 c.c.	1123100000	

3/24/17	18	±	+ 1.5 c.c.	
4/14/17	8	±	— 2.0 c.c.	1112210000
5/19/17	8	trace	— 2.0 c.c.	0000000000

Treatment November 1, 1916, to May 19, 1917:

6 intravenous injections salvarsan
11 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/5 to 1/2 mg.).
18 injections mercury.

Results: Patient returned to work in February, 1917, feeling entirely well and energetic. His headaches and numbness disappeared after the second intraspinal injection and he had no more attacks of aphasia. For the past two years he has been employed by the government and has been able to attend to his work without difficulty.

Case 3. Syphilitic Meningitis

N., age 26. Chancre in May, 1917, followed by fever, dull headache and sore throat three weeks later. Treatment: two courses of salvarsan of six injections each with mercury by injection and by mouth for several months. In June, 1918, he developed photophobia. On examination it was found he had optic edema with beginning atrophy. Aside from nervousness he complained of no other symptoms. Physical examination showed unequal, irregular pupils with sluggish light reflex; the deep reflexes of the upper extremity were more active on the right side than on the left; the patellar jerks were sluggish but equal and the left Achilles jerk was absent.

		Cerebrospinal Fluid			
Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
7/16/18	140	3+	4+ 0.2 c.c.	5555431000	7/19/18 —
7/31/18	116	2+	4+ 0.2 c.c.		8/10/18 —
8/10/18	53	2+	4+ 0.4 c.c.		
8/31/18	20	+	4+ 0.4 c.c.		
10/ 2/18	10	+	4+ 0.6 c.c.	1233210000	
10/26/18	2	trace	3+ 0.6 c.c.		
12/ 4/18	5	trace	2+ 0.8 c.c.		
1/ 8/19	3	trace	4+ 1.5 c.c.	1122100000	
1/29/19	4	—	— 2.0 c.c.		
2/12/19	2	—	— 2.0 c.c.	1111000000	

Treatment from July 22, 1918, to February 12, 1919:

10 intravenous injections salvarsan.
9 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/10 to 1/3 mg.).

Results: His ocular condition responded quickly to treatment and he has no difficulty now except that his eyes tire when he reads for a long time; nervousness has disappeared and he is in excellent physical condition. Has gained 18 pounds in weight.

I see from time to time patients shortly after the secondary stage who give histories of obstinate headaches, vague phobias, depression, irritability, loss of memory and other mental symptoms. These patients have received active treatment since the early stage of their infection. They have been thoroughly dosed with mercury and salvarsan with little impression on their symptoms or Wassermann reaction. They usually show some alteration in their pupillary reactions and deep reflexes. The spinal fluid may reveal a high cell count with strong globulin and Wassermann reactions. A paretic gold sol curve may be present, as in case 4.

CASE 4. PREPARESIS (?)

D., age 36, dentist. Chancre of index finger and secondaries in February, 1913. Treatment: 12 injections of salvarsan, 46 injections mercury salicylate, 25 injections gray oil, several months of mixed treatment. His Wassermann was negative on several occasions but with cessation of treatment became positive again. Patient was very apprehensive and nervous most of the time. He passed from observation for a year and when seen in May, 1916, was nervous and excitable; his pupils were irregular, slightly unequal, but reacted promptly to light and accommodation. All the deep reflexes were hyperactive, the left more so than the right.

Cerebrospinal Fluid					
Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
6/ 3/16	172	3+	4+ 0.2 c.c.	5555430000	2/20/13 ++++
6/24/16	116	4+	4+ 0.2 c.c.		6/ 2/13 —
7/21/16	45	3+	4+ 0.4 c.c.		2/21/14 ++
8/26/16	10	3+	4+ 0.4 c.c.	5555420000	11/20/14 —
10/ 7/16	8	2+	4+ 0.6 c.c.		2/24/15 ++
11/18/16	12	2+	4+ 0.6 c.c.	5554420000	6/19/15 —
12/ 9/16	9	2+	4+ 0.6 c.c.		9/29/15 ++
1/ 6/17	7	2+	4+ 0.6 c.c.		12/15/15 —
2/10/17	10	2+	4+ 0.6 c.c.	5555432000	5/20/16 +++
3/31/17	9	2+	4+ 0.6 c.c.		8/26/16 —
4/28/17	6	2+	3+ 0.6 c.c.		10/28/16 —
6/19/17	0	+	3+ 0.8 c.c.	5555442100	11/18/16 —
7/ 7/17	5	+	4+ 1.0 c.c.		4/28/17 —
8/ 3/17	3	±	2+ 1.0 c.c.		1/12/18 —
10/ 6/17	3	±	4+ 1.5 c.c.	5555421000	7/27/18 —
11/24/17	2	±	3+ 1.5 c.c.		2/12/19 —
12/22/17	1	±	4+ 1.5 c.c.		
1/12/18	6	±	4+ 1.5 c.c.		
2/ 2/18	2	±	4+ 1.5 c.c.		
3/23/18	2	±	4+ 1.5 c.c.	5554421000	
4/13/18	4	±	2+ 1.5 c.c.		
5/ 4/18	1	±	3+ 1.5 c.c.		
6/15/18	1	±	3+ 1.5 c.c.	4455431000	
7/27/18	3	±	4+ 1.5 c.c.		
9/11/18	2	±	4+ 2.0 c.c.	2223100000	
11/ 9/18	2	±	4+ 2.0 c.c.		
12/ 7/18	2	±	4+ 2.0 c.c.	1223100000	

1/11/19	3	±	4+ 2.0 c.c.	
2/12/19	1	trace	— 2.0 c.c.	1233210000

Treatment from June 8, 1916, to February 12, 1919:
- 4 intravenous injections salvarsan. This treatment had to be discontinued owing to severe reactions.
- 33 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/10 to ½ mg.).
- 12 injections of mercury; several courses of potassium iodide and mixed treatment.

Results: Patient feels perfectly well, is free from nervousness and excitability and does his work without effort.

In these cases response to treatment is slow and only after prolonged use of intraspinal injections do we obtain modified reactions. The symptoms abate or disappear only to return when treatment is discontinued. The slow therapeutic response is in marked contrast to the earlier types of meningitis and indicates a probable implantation of spirochetes in the brain itself and their relative inaccessibility to the drugs. These cases are, in my opinion, potential paresis and probably are delayed in their progress by the prolonged treatment. In some of them the process is apparently permanently arrested, as in case 5.

CASE 5. PREPARESIS (?)

A., age 42. Infection in 1905; treatment for seven years with mercury internally and by injection. In June, 1915, he had a convulsion and was unconscious for one-half hour. The attack was attributed to colitis and intestinal absorption and treatment directed against this until December, 1915, when he had a second convulsion. At this time he came under observation complaining of physical exhaustion and loss of interest. His mental condition was hazy, he showed memory defects, and was markedly depressed. Pupils unequal in size; margins regular; reaction to light and accommodation prompt. Bladder slow; sexual power poor. Deep reflexes very active, more so on right side. Babinski and clonus present on right side.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
12/18/15	45	3+	4+ 0.1 c.c.	5555542000	12/14/15 ++++
1/26/16	16	+	4+ 0.4 c.c.	5555432000	4/29/16 ++++
2/26/16	3	+	4+ 0.4 c.c.		8/23/16 —
3/ 9/16	6	2+	4+ 0.4 c.c.	4444430000	3/10/17 —
4/19/16	7	2+	4+ 0.4 c.c.		11/24/17 —
5/ 2/17	0	±	± 1.5 c.c.	1112332000	2/ 2/18 —
6/13/17	2	±	2+ 1.0 c.c.		12/ 5/18 —
7/27/17	2	±	3+ 1.5 c.c.	1123321000	3/25/19 —
3/16/18	2	±	4+ 2.0 c.c.		
4/24/18	2	±	3+ 2.0 c.c.	1122100000	

6/19/18	2	±	± 2.0 c.c.	1111000000
3/25/19	2	—	— 2.0 c.c.	0000000000

Treatment from December 29, 1915, to June 19, 1918:
11 intravenous injections salvarsan.
17 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/12 to 1/4 mg.).
34 injections mercury, several courses of potassium iodide and mixed treatment.

Results: During the past year patient has been unusually strong and well. He has had no convulsions; his mental depression has disappeared and his memory is good. He takes an active interest in his work and is able to concentrate and apply himself to exacting legal work as well as formerly. His bladder has returned to normal and his sexual power has improved.

The hope of arresting the degenerative process lies in early recognition and a persistence in treatment. We are certainly justified by the results obtained in combating this serious type of early encephalitis by the most intensive methods at our command.

In the following charts (Cases 6 and 7) the amount and duration of treatment is shown. These patients are practically free from all mental or physical symptoms, are active in their usual vocations and are only aware of an abnormal state by reason of the persistent positive Wassermann reaction in the fluid. Are we justified in subjecting patients of this type to further treatment in the hope of reversing the Wassermann reaction or must we rest satisfied with clinical cures and hope that time and the body defenses will cause the final disappearance of the reaction? A definite reply to these queries may only be expected after years of accurate observation.

CASE 6. PREPARESIS

H., age 38. Chancre and secondaries skin and mouth in 1904. Internal treatment until 1910 when he developed left external rectus paralysis and suffered from shooting pains in legs and cramps in calves. In 1912 complained of tingling in legs. Came under observation in December, 1912. His reflexes were hyperactive, more so on right side; co-ordination perfect; no sensory changes; station and gait normal. Pupils regular in outline and equal; right slightly sluggish to light.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
12/12/13	26	2+	4+ 0.2 c.c.	5555554100	12/20/12 ±
6/ 9/14	10	2+	4+ 0.4 c.c.		6/ 9/14 ±
9/ 9/14	8	2+	4+ 0.4 c.c.		12/21/14 ±
9/25/14	5	2+	4+ 0.4 c.c.		5/21/15 ±
10/21/14	3	2+	4+ 0.4 c.c.		9/10/15 ±

12/21/14	38	2+	4+	0.4 c.c.	5555555420	1/12/16 —
1/15/15	30	2+	4+	0.4 c.c.		3/14/17 —
4/ 6/15	0	2+	4+	0.4 c.c.		3/ 6/18 —
5/21/15	1	2+	4+	0.4 c.c.		1/15/19 —
7/ 8/15	12	2+	4+	0.2 c.c.	5555555420	
9/10/15	4	2+	4+	0.2 c.c.		
10/ 9/15	0	4+	4+	0.2 c.c.		
11/ 6/15	2	3+	4+	0.2 c.c.		
12/15/15	3	3+	4+	0.2 c.c.		
1/12/16	2	4+	4+	0.4 c.c.	5555555420	
3/29/16	11	3+	4+	0.4 c.c.		
4/26/16	9	3+	4+	0.4 c.c.		
6/ 3/16	8	3+	4+	0.4 c.c.		
7/ 8/16	12	2+	4+	0.4 c.c.		
9/13/16	10	2+	4+	0.4 c.c.		
10/24/16	19	3+	4+	0.2 c.c.	5555555530	
12/20/16	18	3+	4+	0.2 c.c.		
1/31/17	11	3+	4+	0.2 c.c.		
3/14/17	12	4+	4+	0.2 c.c.		
4/25/17	9	3+	4+	0.2 c.c.		
6/16/17	5	4+	4+	0.4 c.c.		
10/ 3/17	38	4+	4+	0.4 c.c.	5555555410	
11/21/17	3	4+	4+	0.4 c.c.		
12/24/17	1	2+	4+	0.4 c.c.		
3/ 6/18	5	2+	4+	0.4 c.c.		
4/17/18	5	+	4+	0.4 c.c.		
7/24/18	6	2+	4+	0.4 c.c.	5555555420	
8/22/18	4	2+	4+	0.4 c.c.		
9/18/18	7	2+	4+	0.4 c.c.		
10/30/18	14	4+	4+	0.2 c.c.		
12/ 4/18	9	4+	4+	0.2 c.c.	5555543100	
1/15/19	5	3+	4+	0.2 c.c.	5555543100	

Treatment January 6, 1913, to January 15, 1919:

1 intramuscular injection salvarsan.
44 intravenous injections salvarsan.
69 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/4 to 1/3 mg.).
Several courses of mercury injections and potassium iodide and mixed treatment.

Results: Patient claims that he feels entirely well mentally and physically. He does the heavy work of an engineer and never loses a day except when he comes for treatment. His pupils and reflexes remain unchanged.

Case 7. Paresis

C., age 46. Genital sore 16 years ago. Mercury pills for two years. Eight years ago alteration in personality evidenced by change in domestic relations—desired on several occasions to divorce his wife insisting that it was his right to do so. During past four years nervous and irritable; handwriting less steady; failure of sexual power; pupils unequal, irregular and sluggish to light; deep reflexes hyperactive; no headaches or convulsions.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
11/30/17	102	4+	4+ 0.2 c.c.	5555554320	11/30/17 ++++
12/15/17	56	4+	4+ 0.2 c.c.		3/ 9/18 ++++
12/29/17	33	4+	4+ 0.2 c.c.	5555554320	8/10/18 ++++
1/26/18	7	3+	4+ 0.2 c.c.		12/16/18 ++++
3/ 9/18	6	2+	4+ 0.2 c.c.	5555554320	
4/17/18	2	4+	4+ 0.2 c.c.		
6/ 8/18	4	2+	4+ 0.2 c.c.	5555554320	
8/10/18	3	2+	4+ 0.2 c.c.	5555543100	
10/ 4/18	2	±	4+ 0.2 c.c.		
11/13/18	3	±	4+ 0.2 c.c.		
12/21/18	4	+	4+ 0.2 c.c.	5555431000	

Treatment from November 30, 1917, to December 21, 1918:

19 intravenous injections salvarsan.
19 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/5 to 1/3 mg.).
11 injections mercury. Several courses of potassium iodide and mixed treatment.

Results: Patient states that he has improved in feeling of general wellbeing; can work longer without fatigue; handwriting is more steady and uniform. Nervousness and irritability have disappeared. He says he now realizes that he was wrong in his attitude toward his wife and treats her with every consideration.

THE TABETIC GROUP OF NEUROSYPHILIS

All syphilitic lesions are reactions to spirochetal invasion. In the skin and accessible tissues their evolution and regression can be followed and interpreted; secondary changes here aside from deformity are usually a matter of small moment. The central nervous system, however, presents more complicated problems in the results due to vessel occlusion and in tract degenerations secondary to focal lesions.

The clinical conception of tabes has been based largely on the results of degeneration in the posterior columns namely, ataxia, loss of reflexes, sensory disturbance and associated disorders of the bladder and sexual apparatus. In the preataxic stage before any of the symptoms enumerated are fully developed and which may be present for years, modern methods of research often reveal conditions which are susceptible of relief by modern therapeutic agents.

The essential lesion in tabes is a posterior root and column degeneration with resulting death of the neurone whether primary or secondary to a meningitis. The creation of a pseudotabes and a true tabes according to their theoretic mode of origin is largely artificial and based on few necropsy findings in the early stage of the process.

A primary neuronal degeneration may occur and may be caused by direct invasion of the posterior roots and columns by the spirochetes. The meningeal reaction in these cases may be absent or slight and may be secondary to the neuritis. The response to treatment in such cases would depend largely on when the condition is recognized and the accessibility to the spirochetes of the specific drugs. But, if we are permitted to make any deductions from the fluid findings as to the character of the central lesion, we must conclude that in the majority of cases of progressive tabes meningeal reactions are present. Most of the earlier work is based chiefly on observations which antedated our exact knowledge acquired by biological examinations and it is a matter of academic interest only as to which is the primary change. The intensity of the reaction furthermore is not necessarily dependent on the age of the process as we have frequently found a cell count of over a hundred in tabes of twenty years' duration. Reactions of varying degrees of severity occur in all tissues which harbor spirochetes; these may continue to multiply and involve new areas for an indefinite time. Advanced posterior column degeneration is, of course, irremediable, but many of the associated symptoms as pain or crises are due to an accompanying meningitis and insofar can be relieved by treatment. Tabes progresses because the cause persists; new segments are involved by fresh invasions of the organism. It is clinically impossible to differentiate the so-called pseudotabes from its true prototype as both have Argyll Robertson pupils, absent deep reflexes, sensory disturbances, etc. Aside from symptoms from advanced degeneration in the lower segments of the cord spinal fluid findings are a surer therapeutic guide than clinical symptoms alone. A tabetic with a relatively high cell count and other phases positive can be promised marked amelioration and probably arrest of his degenerative process. To call a case pseudotabes which responds to treatment and the other real tabes which shows no response is illogical. All the classical signs of tabes may be present in a patient where spinal fluid shows active meningeal involvement and these cases give the most striking improvement after treatment, as illustrated in Cases 8, 9, and 10.

CASE 8. TABES DORSALIS

C., age 43. Chancre 20 years ago; secondaries denied. Treatment by inunction over a period of years. Was first seen in February, 1917, when he gave a history of having had shooting pains in his back and thighs, so severe at times that he was confined to his bed. He was nervous, irritable and profoundly depressed, his mental condition interfering with his business activities. On examination he presented Argyll Robertson pupils, ataxia and sensory disturbance. The deep reflexes were absent in the lower extremities and sluggish in the upper. He had some bladder difficulty. For several months he had been intensively treated with salvarsan and mercury, but obtained no relief.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
2/ 7/17	243	4+	2+ 0.2 c.c.	3334430000	5/ 5/17 —
2/14/17	179	4+	4+ 0.4 c.c.	3344441000	7/27/17 —
2/27/17	20	+	4+ 0.4 c.c.		1/30/18 —
3/14/17	10	+	4+ 0.4 c.c.	2333210000	
4/11/17	7	2+	4+ 0.4 c.c.		
5/ 2/17	5	+	4+ 0.6 c.c.		
5/22/17	2	+	4+ 0.8 c.c.		
7/20/17	2	±	+ 1.0 c.c.	1123100000	
8/16/17	4	—	3+ 1.5 c.c.		
10/ 6/17	3	trace	4+ 2.0 c.c.	1122100000	
11/10/17	1	±	± 2.0 c.c.		
1/30/18	2	trace	± 2.0 c.c.	1123210000	
3/23/18	1	±	+ 2.0 c.c.		
5/ 4/18	1	—	2+ 2.0 c.c.	1122100000	
6/22/18	1	—	± 2.0 c.c.		
9/11/18	2	trace	— 2.0 c.c.		
11/20/18	1	trace	— 2.0 c.c.	1111000000	

Treatment from February 3, 1917, to November 16, 1918:
18 intravenous injections salvarsan.
19 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/5 to 1/2 mg.).
Several courses of mercury injections and potassium iodide.

Results: There has been complete disappearance of the pains and ataxia; he is no longer depressed and is able to conduct his business with his former energy. Bladder is occasionally slow. He has gained 25 pounds in weight and says his health is excellent.

CASE 9. TABES DORSALIS

R., age 40. Initial lesion in 1905 followed by secondaries in the mouth and skin. In March, 1913, his chief complaints were girdle sensation, shooting pains in lower extremities and difficulty in walking, sexual power was weak and bladder slow. Patient was exceedingly irritable, depressed and very nervous. Examination showed Argyll Robertson pupils, absent knee and ankle jerks, Romberg, and marked ataxia.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Serum*
3/11/13	70	+	4+ 0.4 c.c.	3/11/13 ++++
11/21/13	46	+	4+ 0.4 c.c.	9/ 4/13 ++++
4/17/14	0	—	4+ 0.6 c.c.	5/ 1/14 +

5/29/14	0	—	4+ 0.8 c.c.		6/ 9/14 —
6/15/14	0	—	4+ 0.8 c.c.		4/21/15 —
7/10/14	0	—	2+ 1.0 c.c.		
8/15/14	0	—	4+ 2.0 c.c.		
5/18/15	0	—	— 2.0 c.c.		

Treatment from March 13, 1913, to August 15, 1914:
18 intravenous injections salvarsan.
11 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 3/4 to 1 mg.).
7 injections mercury.

Results: Patient was intolerant to mercury and received no benefit from 12 intravenous injections of salvarsan. After the intraspinal treatments the leg pains and girdle sensation disappeared; his bladder and sexual power improved. He gained 50 pounds in weight and his ataxia was scarcely perceptible; he was able to walk four or five miles without assistance or fatigue. For five years he has been back at his work and has had no relapse.

CASE 10. TABES DORSALIS

S., age 36. Initial lesion in 1906; no secondaries. Was first seen December 9, 1915. For seven years had had sharp shooting pains in his legs, could not run and was ataxic especially when climbing stairs. For the past two years bladder had become very slow with frequent and difficult micturition. He had Argyll Robertson pupils, a Romberg, absent deep reflexes and a band of anesthesia in the mammary region.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
1/ 8/16	42	2+	4+ 0.2 c.c.	2223333000	12/10/15 ++++
3/16/16	6	+	2+ 0.4 c.c.	1113332000	4/29/16 ++++
5/16/16	3	2+	+ 0.4 c.c.	1112321000	6/24/16 +++
6/ 3/16	14	+	4+ 0.6 c.c.		9/ 9/16 —
8/30/16	8	+	4+ 0.8 c.c.		1/10/17 —
11/21/16	3	+	3+ 1.0 c.c.	1123210000	7/24/18 —
12/13/16	10	±	3+ 1.0 c.c.		1/ 9/19 —
1/10/17	7	+	3+ 1.0 c.c.		
2/27/17	8	+	2+ 1.0 c.c.	1122100000	
10/10/17	5	trace	3+ 1.0 c.c.		
1/30/18	1	±	+ 1.0 c.c.	1122100000	
3/ 6/18	6	trace	+ 1.0 c.c.		
5/15/18	2	trace	2+ 1.5 c.c.		
6/19/18	2	trace	2+ 1.5 c.c.	1122100000	
7/24/18	1	±	2+ 1.5 c.c.		
9/ 5/18	2	trace	4+ 2.0 c.c.	1122100000	
1/29/19	0	trace	— 2.0 c.c.	1122100000	

Treatment from December 15, 1915, to January 29, 1919:
9 intravenous injections salvarsan.
30 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/10 to 1/3 mg.).
21 injections mercury.

Results: Is now free from all pain but still slightly ataxic when going down stairs or turning suddenly. He says his general health is excellent, that he is able to work every day and suffers from no undue fatigue. His bladder is only occasionally slow.

In the tabetic group we may include (1) arrested cases with Argyll Robertson pupils, absent deep reflexes and anesthetic areas with a negative blood and spinal fluid. Several of these cases have been observed and controlled for three to five years with no clinical or serologic change. Stationary or abortive tabes with a negative fluid serology is a contraindication to the use of intraspinal therapy. Salvarsanized serum is introduced into the spinal canal to combat active lesions. If the reactive phenomena are absent it is fair to assume that the organisms have disappeared after causing a definite and limited lesion. The degeneration in question is nonprogressive as a result of previous treatment or is spontaneously cured by the normal defenses of the body. (2) Preataxic tabes with pupillary changes, absent or sluggish and unequal deep reflexes, bladder or sexual weakness, pains and some disturbance of station with increasing fatigue in walking. Here we find a fairly high cell count, positive globulin, positive Wassermann reaction and a leutic curve. The prognosis is relatively good and we can predict arrest of the process with relatively little secondary degeneration. If permitted to progress would such cases become ataxic? Probably, as the symptoms point to posterior root or column involvement. (3) Advanced cases with ataxia, Romberg, bladder and sexual weakness, pains, crises, etc. The fluid may show a relatively low cell count with the Wassermann reaction positive in larger quantities, an excess of globulin and a luetic, or it may be quite negative, curve. Intraspinal therapy offers less hope of relief in their patients because of advanced degeneration and the slight meningitis. In low tabes, too, there is danger of an added irritant to the cord and the possibility of an increase in symptoms. In these cases only the Swift-Ellis method should be used. In high tabes there is less inconvenience from the injected serum and the treatment may be long continued with complete arrest of the process. (4) More or less advanced tabes with a cell count varying from 20 to 100 or more, a positive Wassermann reaction in the high dilutions and a paretic gold sol curve. These cases may or may not show mental symptoms, but offer an unfavorable prognosis, as the reactions respond slowly to treatment if at all (Case 11).

CASE 11. TABOPARESIS (?)

M., age 37. Chancre and secondaries 13 years ago. Treatment by mouth and inunction for three and a half years. For years has had lancinating pains in the legs and a sensation of numbness above the right knee. For several months has had dull frontal headaches; was easily fatigued and excited and was always very nervous. Examination revealed Argyll Robertson pupils; ankle jerks absent; left patellar jerk absent, right very sluggish. No memory defect.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
7/20/17	17	4+	4+ 0.2 c.c.	5555554200	7/20/17 ++++
8/23/17	8	4+	4+ 0.2 c.c.		2/20/18 +++
9/12/17	7	3+	4+ 0.2 c.c.	5555543100	7/24/18 ++
10/ 3/17	4	+	4+ 0.2 c.c.	5555421000	12/11/18 +
11/21/17	4	2+	4+ 0.2 c.c.		
12/19/17	3	+	4+ 0.2 c.c.	5555431000	
1/23/18	4	2+	4+ 0.2 c.c.		
2/20/18	1	3+	4+ 0.4 c.c.		
3/27/18	3	+	4+ 0.4 c.c.	5555421000	
4/24/18	4	+	4+ 0.4 c.c.		
6/24/18	3	+	4+ 0.4 c.c.		
7/24/18	2	±	4+ 0.4 c.c.	5555431000	
10/ 9/18	4	±	4+ 0.4 c.c.		
12/11/18	3	±	4+ 0.4 c.c.		
1/15/19	5	±	4+ 0.4 c.c.		
2/12/19	2	±	4+ 0.4 c.c.		
2/25/19	2	±	4+ 0.4 c.c.	5554421000	

Treatment from July 23, 1917, to February 25, 1919:
21 intravenous injections salvarsan.
20 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/4 to 1/2 mg.).
Several courses mercury.

Results: Clinically the pains have ceased and the patient is no longer nervous and has much more endurance. There has been no progress in his somatic signs.

Table II gives the serologic findings in patients who presented the typical syndrome of tabes, i. e., Argyll Robertson pupils, absent deep reflexes, sensory changes with ataxia and impairment of sphincter control. The increased cell count shows the accompanying meningitis.

The importance of the systematic examination of the eye grounds in all stages of lues should be emphasized by every teacher of syphilis, as pathologic changes may be present with slight subjective symptoms or visual impairment. The hope of preventing optic atrophy or arresting it in its early stages depends largely on such systematic examinations. Every case of optic atrophy whether primary

TABLE II

SEROLOGY IN TABES

NO.	CELLS	GLOBULIN	WASSERMANN	GOLD SOL	SERUM
1	60	++++	++++ 0.1	1123320000	—
2	64	+++	++++ 0.4	1233210000	+++
3	72	+++	++++ 0.4	4433210000	±
4	73	+++	++++ 0.2	1123321000	++++
5	73	+	++++ 0.4	1123210000	++++
6	75	+++	++++ 0.5	2233210000	+
7	81	++++	++++ 0.4	1111000000	—
8	93	++++	++++ 0.2	1122321000	—
9	100	++++	++++ 0.2	5555542000	++++
10	120	++++	++++ 0.1	2223310000	++++
11	150	+++	++++ 0.1	5555543000	++++
12	150	++++	++++ 0.2	1123210000	+++
13	172	+++	++++ 0.2	5555543100	+
14	175	+++	++++ 0.4	1123320000	+
15	175	++++	++++ 0.1	1233210000	++++
16	175	++++	++++ 0.2	1123221100	++++
17	193	++++	++++ 0.2	3333343100	++++
18	230	++++	++++ 0.1	1233210000	+++
19	247	++++	++++ 0.2	1123321000	—
20	268	+++	++++ 0.2	5555431000	++
21	315	+++	++++ 0.2	5555543100	+

N. B.: The cases with the paretic curve and strongly positive Wassermann reaction are potential taboparesis. None of these cases, however, had at the time of examination clinical indications of mental involvement.

or a part of the tabetic or paretic syndrome demands an examination of the spinal fluid at the earliest possible moment. This statement in my opinion admits of no argument or debate. In case the spinal fluid shows a primary or associated meningitis with other positive phases of syphilis a method of treatment should be begun which offers hope of arresting the destructive process. Experience has shown how little may be expected from mercury and potassium iodide or salvarsan intravenously. Persistence in methods demonstrated to be futile or of little value is wasted effort and loss of valuable time. The atrophy progresses and a stage is reached where relief is impossible. Theoretic objections to intraspinal therapy in cases which show the fluid findings of syphilitic meningitis are based on ignorance and prejudice and closely approach criminal negligence. Intraspinal treatment in optic atrophy is indicated where the fluid shows a meningitis with the positive phases of syphilis. When present with other types of neurosyphilis the fluid findings may not accurately reflect the changes in the optic nerve or its meningeal coverings. The optic atrophy is, however, the condition which calls for immediate relief. The integrity of an important organ is involved and admits of no delay in futile efforts. In advanced atrophy with negative or practically negative findings in the fluid little can be expected from treatment of any kind. Persistent intraspinal treatment when indicated by the fluid findings can arrest the progress of many cases and preserve the remaining vision. Theoretical arguments that the serum does not reach the invaded nerve are invalidated by the results of treatment. Employment of a proper technic medicates outside the spinal canal one third of the entire spinal fluid when this is returned by gravity. Salvarsanized serum directly introduced into the lumbar subarachnoid space diffuses itself more slowly and accomplishes less then when diluted outside the body with a large quantity of fluid.

The results obtained in cases like 12, 13, and 14 overthrow the contentions of those who oppose the treatment because of physiologic arguments.

CASE 12. OPTIC ATROPHY AND TABES

B., age 45. Syphilis and gonorrhea denied. In January, 1917, he gave the following history: For 13 years had had intermittent attacks of severe shooting pains and for two years similar pains in the chest and upper extremities. Four years ago nervous breakdown with suicidal tendencies. Bladder and sexual weakness for three or four years. Impairment of vision for two years. When first seen could only distinguish light and dark with the right eye and could only read large print with the left. Pupils were unequal, irregular and gave the Argyll Robertson reaction. All deep reflexes upper and lower extremities were absent.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
1/12/17	63	3+	4+ 0.2 c.c.	5554431000	1/10/17 +++
2/17/17	9	2+	4+ 0.4 c.c.		1/ 5/18 ++
3/31/17	7	+	4+ 0.6 c.c.	1133310000	1/23/19 +
4/25/17	5	±	2+ 0.6 c.c.		
5/29/17	6	+	4+ 0.8 c.c.		
10/ 9/17	3	+	± 1.0 c.c.	1123210000	
11/ 3/17	5	+	3+ 1.5 c.c.		
1/ 9/18	3	±	± 1.5 c.c.	1123210000	
2/20/18	1	trace	+ 1.5 c.c.		
3/13/18	2	±	2+ 2.0 c.c.	1123210000	
4/ 6/18	1	—	4+ 2.0 c.c.		
5/25/18	3	trace	4+ 2.0 c.c.	1123210000	

6/22/18	2	trace	3+ 2.0 c.c.	
9/28/18	2	trace	2+ 2.0 c.c.	
10/26/18	3	trace	2+ 2.0 c.c.	1112100000
1/ 4/19	2	trace	± 2.0 c.c.	
1/29/19	0	trace	— 2.0 c.c.	1112100000

Treatment from January 15, 1917, to February 26, 1919:

22 intravenous injections salvarsan.
23 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/10 to 1/2 mg.).
32 injections mercury and courses of potassium iodide.

Results: Pains, nervousness, and suicidal tendencies have disappeared; his bladder has become normal and his sexual power has improved. He states that the vision in his right eye is somewhat better and that of left eye considerably more acute than two years ago. From the ophthalmologist's report the vision in his right eye is 3/200 and in his left 18/40.

Case 13. Optic Atrophy

C., age 52. Infection 20 years ago. Treatment for nine months by mouth. No symptoms until 1912 when he noticed failure of vision. Was first seen in May, 1914, when he showed Argyll Robertson pupils, advanced atrophy of left optic nerve and a contracted field on the right side. His deep reflexes were equal and active; there was no disturbance of his bladder or sexual function. He was an excessive smoker and addicted to the use of alcohol. The ophthalmologic report was as follows: "No perception of light in the left eye; he has normal vision in right eye with refractive error corrected but an optic nerve that looks as white as that of left eye. He has a quadrant sector defect (lower nasal) of the visual field in his right eye with some limitation of the field."

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
5/25/14	60	4+	4+ 0.1 c.c.		5/22/14 —
6/18/14	21	4+	4+ 0.4 c.c.		6/ 4/15 —
7/ 8/14	22	4+	4+ 0.6 c.c.		11/ 4/16 —
7/29/14	11	4+	4+ 0.8 c.c.		
9/ 4/14	5	4+	— 2.0 c.c.		
11/12/14	6	4+	— 2.0 c.c.		
6/ 2/15	0	2+	— 2.0 c.c.		
11/14/16	4	2+	— 2.0 c.c.	1123320000	

Treatment from May 28, 1914, to November 12, 1914:

5 intravenous injections salvarsan.
6 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/4 to 1/3 mg.).

Results: A report dated November 20, 1916, reads that his right field is exactly the same as it was at the time of his examination in May, 1914. His sight is very nearly normal. A letter from the patient February 5, 1918, states that his general health is very good and his eye sight stationary.

CASE 14. OPTIC ATROPHY

C., age 50. Syphilis denied. In June, 1914, double vision, pains in legs and slight ataxia. In January, 1915, presented Argyll Robertson pupils and atrophy of both optic nerves, more marked in right eye. Deep reflexes absent.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
1/25/15	82	2+	4+ 0.4 c.c.	2244421000	1/25/15 —
2/25/15	16	2+	4+ 0.4 c.c.		2/ 2/15 —
3/22/15	17	2+	4+ 0.4 c.c.	2234321000	1/19/16 —
4/ 5/15	10	2+	4+ 0.4 c.c.		
6/28/15	0	+	4+ 0.8 c.c.	2233210000	
8/ 2/15	0	2+	4+ 0.4 c.c.		
9/10/15	0	2+	4+ 0.6 c.c.	1233100000	
10/23/15	3	+	4+ 0.4 c.c.		
1/19/16	2	±	4+ 1.0 c.c.	1112210000	

Treatment from January 25, 1915, to January 19, 1916:
3 intravenous injections salvarsan.
12 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/5 to 1/4 mg.).
Several courses mercury and potassium iodide.

Results: The late Dr. Marple's report dated March 24, 1915, read as folloys: "On February 5 patient's vision was 20/70 minus. Today it was 20/40 and with correction almost fully 20/30." Under date of January 20, 1916, he reported: "The vision is in every way normal." A letter received from the patient in March, 1918, stated that he was feeling well and at work all the time. His mind was clearer and he had had no pain and no fatigue after exercise. His vision remained as above.

Paresis is readily diagnosticated when degeneration of the brain cells is sufficiently advanced to cause marked mental symptoms, disorientation, speech disturbance, expansive ideas, and convulsions. The blood and spinal fluid in these cases practically always yield a strongly positive Wassermann reaction, the latter in high dilutions in the spinal fluid with a strong globulin content and a gold sol paretic curve. The number of cells in the fluid is variable; in treated cases they may amount to twenty or less. In the majority of fluids examined the cell count is the first of the phases to be influenced by treatment. Where intensive courses of salvarsan intravenously have been given before lumbar puncture was made a low cell count is often found, but not always.

The data accumulated as to the average period when paresis occurs after the primary infection are based largely on the time when obtrusive symptoms appear. Psychiatrists and neurologists as a rule see cases only in this stage and have little or no experience with patients showing vague or transitory symptoms which may have been present for years previously and wrongly interpreted. Although the literature of psychiatry often recites the occurrence in the previous history of paretics of neurasthenic states and passing symptoms indicating mental disturbance, little weight has been attached to them by the patient or his medical adviser.

Since systematic examination of the spinal fluid in secondary syphilis too little time has elapsed to enable us to speak with certainty as to the type of early neurosyphilis which may develop paresis. We have fortunately spinal fluid tests which indicate the probable site of the syphilitic infection in the central nervous system and a large number of examinations showing to what degree these reactions resist therapeutic attacks which influence the more superficial types of neurosyphilis. Accurate clinical serological observations over a period of five years in certain of these cases have developed a considerable degree of confidence in the prognostic value of the tests. A spinal fluid which shows a positive Wassermann reaction in the lower dilutions with a leutic gold sol curve is of favorable prognostic import as regards the possible development of paresis. On the contrary the persistence of the Wassermann reaction in the high dilutions with a paretic curve is of graver significance.

TABLE III

SEROLOGY IN PARESIS

NO.	CELLS	GLOBULIN	WASSERMANN	GOLD SOL	SERUM
1	0	++++	++++ 0.2	5555555400	++++
2	1	+++	++++ 0.2	5555541000	++++
3	2	+	++++ 0.6	5444420000	±
4	3	+++	++++ 0.1	5555543000	+++
5	4	++	+++ 0.2	5555442100	+++
6	8	++++	++++ 0.2	5555554310	+
7	9	+	++++ 0.2	5555442100	+
8	18	++++	++++ 0.2	5555543210	++++
9	22	++++	++++ 0.2	5555543100	++++
10	29	++++	++++ 0.2	5555554310	++++
11	40	+++	++++ 0.2	5555542000	++++
12	41	+++	++++ 0.2	5555554310	++++
13	55	++++	++++ 0.2	5555543100	++++
14	55	++	++++ 0.2	5555555540	+++
15	60	++++	++++ 0.2	5555555200	—

Table III Continued

Serology in Paresis

NO.	CELLS	GLOBULIN	WASSERMANN	GOLD SOL	SERUM
16	62	++++	++++ 0.1	5555543100	++++
17	67	++++	++++ 0.2	5555541000	++++
18	68	++++	++++ 0.2	5555555431	++++
19	70	++++	++++ 0.4	5555554310	±
20	73	++++	++++ 0.2	5555544300	++++
21	75	++++	++++ 0.4	5555543200	++++
22	61	++++	++ 0.2	5555431000	++++
23	80	++++	++++ 0.2	5555542000	++++
24	82	++++	++++ 0.2	5555443100	++++
25	85	++++	++++ 0.2	5555555200	++
26	85	+++	++ 0.2	5555554300	++++
27	86	++++	++++ 0.2	5555543100	++++
28	90	++++	++++ 0.1	5555543100	++++
29	96	++	++++ 0.2	5555442100	++++
30	102	++++	++++ 0.2	5555554320	++++
31	110	++	++++ 0.1	5555544100	++++
32	119	++++	++++ 0.2	5555543000	++++
33	121	++++	++++ 0.2	5555542000	+++
34	125	++++	++++ 0.1	5555554400	++++
35	140	++++	++++ 0.1	5555554210	++++
36	140	+	++++ 0.2	5555430000	—
37	168	++++	++++ 0.2	5555555431	++++
38	180	++++	++++ 0.2	5555543200	++++
39	202	++++	++++ 0.2	5555543100	++++
40	250	++++	++++ 0.2	5555543100	++++

The probable development of paresis should always be kept in mind when little or no impression can be made on the Wassermann reaction in the spinal fluid by persistent intraspinal treatment. Symptoms due to the coexisting meningitis or to lesions in the superficial layers of the cortex may disappear and remissions of longer or shorter duration be induced by treatment, but as to the possibility of permanent cures in deep-seated encaphalitis little of a positive assertion can be made. Limited involvement of the brain may exist for years with little effect on the intellectual processes and show the spinal fluid findings of paresis. The progress of such cases is slow and they may appear normal in every respect. Potentially paresis is present in them and only long-continued observations controlled by laboratory tests can reveal the final outcome. Intraspinal treatment modifies the course of well-developed paresis and often renders the individual capable of resuming for a time his activities (see Case 15).

Case 15. Paresis

K., age 45. Syphilis denied; gonorrhea 14 years ago. Was first seen September 13, 1917, when he exhibited delusions of grandeur, speech disturbance, and memory defects. His employer had complained of his carelessness and inattention to work for the past several months. He frequently fell asleep at his desk. On examination he was found to have rigid pupils, hyperactive reflexes, facial tremor and writing defects. His sphincter control was normal; he gave a history of perverted sexual desires for several months.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
9/15/17	80	4+	4+ 0.2 c.c.	5555542000	9/15/17 ++++
10/13/17	16	4+	4+ 0.2 c.c.		5/25/18 ++++
11/10/17	10	4+	4+ 0.2 c.c.	5555431000	1/ 8/19 ++++
12/ 8/17	8	3+	4+ 0.2 c.c.		
1/26/18	7	3+	4+ 0.2 c.c.		
2/20/18	7	2+	4+ 0.2 c.c.	5555421000	
3/30/18	3	+	4+ 0.2 c.c.		
4/27/18	3	+	4+ 0.2 c.c.		
5/18/18	2	+	4+ 0.2 c.c.	5555431000	
7/12/18	3	±	4+ 0.2 c.c.		
8/14/18	2	±	4+ 0.2 c.c.	5555421000	
10/ 2/18	2	±	3+ 0.2 c.c.		
11/13/18	1	±	4+ 0.2 c.c.		
12/11/18	4	±	4+ 0.2 c.c.		
1/ 8/19	2	±	4+ 0.2 c.c.	5555431000	
2/12/19	1	±	2+ 0.2 c.c.	5555431000	

Treatment from September 13, 1917, to February, 12, 1919:

29 intravenous injections salvarsan.
23 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/5 to 1/2 mg.).
Several courses of mercurial injections and potassium iodide.

Results: His mental condition is totally different. He has lost his delusions of grandeur and his speech has improved so that he is able to make long addresses without difficulty. For eight months he has been carrying on trying war work without inconvenience. He has no gross memory defects but his wife says he is forgetful at times. Sexually he has returned to normal.

The remission in symptoms is doubtless due to the control of the meningitis and more superficial lesions. The continued activity in the deeper lesions leads to slow degeneration of the brain cells and ultimately to complete dementia and death. Reports made from time to time regarding rapid changes in the Wassermann reaction and the gold sol test by intraventricular or other treatment are based on limited observations and incorrect laboratory tests.

The results obtained by the intraspinal treatment in preparesis when sufficiently prolonged at times are so encouraging that we feel justified in carrying it out to the limit of the patients' endurance. They are entitled to the only procedure which offers any hope of benefit if it is unattended by risk. We feel that with the careful technic now employed and with the proper preparatory treatment that danger to the patient's life or possible damage to the cord or brain has been entirely eliminated. Such treatment by the inexperienced without laboratory facilities and proper serologic control will certainly fail and cause the procedure to be condemned as useless and harmful.

The following miscellaneous group comprises; first, cases of neurosyphilis in which clinical and serologic cure was obtained; second, clinical improvement without serologic cure; and third, neither clinical nor serologic cure.

CASE 16. CEREBROSPINAL SYPHILIS

M., age 38. No history of syphilis. In September, 1915, developed occipital headaches and severe epileptiform seizures. Her pupils were unequal, irregular in outline, and fixed to light. Her deep reflexes were very active, more so on right side.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*		*Gold Sol*	*Serum*
3/ 1/16	86	3+	4+	1.0 c.c.	1112210000	2/29/16 +
4/ 7/16	25	2+	4+	1.0 c.c.		9/23/16 +++
5/ 6/16	11	2+	4+	1.5 c.c.		9/12/17 —
5/27/16	5	+	2+	2.0 c.c.	1123200000	12/ 8/17 —
7/21/16	3	±	2+	2.0 c.c.		5/ 1/18 —
12/16/16	0	+	—	2.0 c.c.		10/26/18 —
7/11/17	3	±	—	2.0 c.c.	0000000000	

Treatment from February 28, 1916, to February 2, 1917:
- 7 intravenous injections salvarsan.
- 8 intraspinal injections (Swift-Ellis, fortified with 1/10 to 1/5 mg.).

Results: Headaches disappeared after the second intraspinal injection. She has had no attacks of epilepsy in the last 14 months. Her weight has increased from 89 pounds at the beginning of treatment to 111 pounds; she has regained her endurance, plays golf and tennis, drives her own car, and seems to be normal in every way.

CASE 17. CEREBROSPINAL SYPHILIS

H., age 31. Multiple chancres 15 years ago. No secondaries. Noticed for nine months a decline in sexual power and some hesitancy in passing urine. Had lost in weight and also noted inequality of pupils and impairment of memory and inability to concentrate. Deep reflexes were all exaggerated. His pupils reacted to light; the left a little more promptly than the right.

	Cerebrospinal Fluid				
Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
1/ 8/16	39	+	4+ 0.2 c.c.	1112320000	1/ 8/16 ++++
2/ 2/16	12	±	4+ 0.2 c.c.	1111220000	10/24/16 ++
6/ 3/16	12	±	4+ 0.8 c.c.	1112200000	12/13/16 —
9/14/16	4	±	4+ 1.0 c.c.		
10/24/16	0	±	4+ 1.5 c.c.		
12/13/16	0	±	3+ 2.0 c.c.		
2/21/17	1	±	± 2.0 c.c.		
4/ 4/17	2	±	— 2.0 c.c.		
5/16/17	0	trace	— 2.0 c.c.		

Treatment from January 8, 1916, to May 16, 1917:

11 intravenous injections salvarsan.

11 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/10 to 1/3 mg.).

Results: Since January, 1917, has been unusually well and has gained in weight; sexual power and bladder have become normal. Thinks his memory is as good as it ever was. Reflexes have become more nearly normal.

CASE 18. CEREBROSPINAL SYPHILIS

M., age 48. Genital lesion in 1906; no secondaries. Took mercury pills for a month. Came in October, 1916, complaining of great depression and syphilophobia. He had been quite irritable for about six months and had occasional occipital headaches about a year. For two weeks feeling of tightness and weakness in calves of legs; numbness in dorsum of left foot. His pupils were found to be unequal and slightly irregular. They reacted promptly but did not hold. The deep reflexes were present and lively, the left more so than the right.

	Cerebrospinal Fluid				
Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
11/ 4/16	83	+	4+ 0.8 c.c.	1123210000	10/31/16 +
2/ 3/17	6	+	4+ 1.0 c.c.	1122100000	2/ 3/17 +
2/28/17	6	+	4+ 2.0 c.c.		8/ 3/17 —
3/21/17	18	±	— 2.0 c.c.		11/17/17 —
4/20/17	10	trace	— 2.0 c.c.		3/30/18 —
5/22/17	1	—	— 2.0 c.c.		5/11/18 —
7/27/17	0	trace	— 2.0 c.c.		
5/11/18	0	±	— 2.0 c.c.	1111000000	

Treatment from October 31, 1916, to July 25, 1917:

11 intravenous injections salvarsan.

5 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/5 to 1/3 mg.).

15 injections mercury and several courses of mixed treatment.

Results: Since January, 1917, depression, headaches and irritability have disappeared. The feeling of tightness in calves of legs and numbness in left foot have also gone. No change in reflexes. Patient is able to take care of a large surgical and consultant practice with ease.

CASE 19. CEREBROSPINAL SYPHILIS

M., age 30. Chancre denied. Secondaries in 1905. Came under observation February 8, 1917. For two years had had frequent attacks of severe shooting pains in hands and lower extremities accompanied by tired languid feeling. For one year had had frequent occipital headaches with weakness in neck; slept badly and was extremely nervous and depressed; was very forgetful and unable to think clearly at times. For past six months had sharp pains in temporal region. Had taken mercury by mouth and injection for two years. Examination showed dilated pupils, right larger than left; reaction to light sluggish; outlines irregular; deep reflexes on the right side hyperactive with Babinski present on that side.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
2/17/17	38	+	4+ 0.2 c.c.	4444420000	2/ 9/17 ±
3/24/17	5	±	4+ 0.6 c.c.		3/25/18 —
			2+ 0.4 c.c.		12/18/18 —
5/29/17	6	±	4+ 0.8 c.c.	1123320000	
			3+ 0.6 c.c.		
6/23/17	0	±	4+ 1.5 c.c.		
			± 1.0 c.c.		
7/27/17	3	+	4+ 1.5 c.c.		
9/26/17	4	±	4+ 2.0 c.c.		
10/24/17	3	+	± 2.0 c.c.		
12/ 5/17	1	±	— 2.0 c.c.		
3/27/18	2	±	— 2.0 c.c.		
12/18/18	0	±	— 2.0 c.c.	1111000000	

Treatment from February 19, 1917, to March 27, 1918:

11 intravenous injections salvarsan.
11 intraspinal injections (Swift-Ellis, fortified with 1/10 to 1/4 mg.).
7 injections mercury.

Results: Pain, headaches, mental depression, insomnia and fatigue have entirely disappeared. Has gained 20 pounds in weight and feels in excellent health.

CASE 20. TABES

X., age 35, nurse. Initial lesion left breast in 1902 followed by cutaneous and mouth lesions. Two months later developed severe generalized headaches with extreme nervousness. Internal treatment for three or four years. From 1911 to 1915 suffered from weakness, extreme fatigue, lack of concentration and difficulty to put thoughts into words. Noticed slight ataxia when going up stairs or walking in the dark.

Came under observation April 3, 1915. Pupils were large, right slightly greater than left; both were irregular in outline and reacted sluggishly to light and accommodation. All the deep reflexes on the left side were absent and on the right side very sluggish, the tendo Achilles on this side being absent.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
4/ 5/15	30	2+	4+ 0.4 c.c.	1112110000	4/ 5/15 +++
8/15/15	47	2+	4+ 0.6 c.c.		12/ 4/15 —
9/10/15	12	+	4+ 0.4 c.c.		1/19/16 —
1/22/16	0	—	4+ 2.0 c.c.		6/21/16 —
3/ 1/16	0	—	3+ 2.0 c.c.		4/ 7/17 —
4/29/16	2	trace	2+ 2.0 c.c.		1/19/18 —
5/27/16	5	+	3+ 2.0 c.c.		
6/30/16	4	±	4+ 2.0 c.c.		
7/28/16	8	±	2+ 2.0 c.c.		
8/23/16	7	±	+ 2.0 c.c.		
9/19/16	3	±	+ 2.0 c.c.		
11/18/16	6	+	+ 2.0 c.c.		
12/20/16	9	±	± 2.0 c.c.		
1/17/17	2	±	± 2.0 c.c.		
2/17/17	1	±	— 2.0 c.c.	1112210000	
3/21/17	2	trace	— 2.0 c.c.		
7/20/17	2	—	— 2.0 c.c.	0000000000	
1/19/18	1	trace	— 2.0 c.c.	0000000000	

Treatment from April 5, 1915, to February 14, 1917:

15 intravenous injections salvarsan.

18 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/10 to 1/5 mg.).

17 injections of mercury and several courses of mixed treatment.

Results: Patient's memory has greatly improved. She is able to work without fatigue and has much more endurance. Has worked for several months on a farm. Her pains and ataxia have disappeared.

CASE 21. CEREBROSPINAL SYPHILIS

R., age 47. Initial lesion in 1890. When seen on June 30, 1913, gave the following history:

Five years ago nervous prostration, insomnia, marked depression with suicidal tendencies, loss of self-respect, bad memory and inability to concentrate. For one year severe headaches and loss of sexual power; bladder slow. Felt very weak and tired, was unable to move left foot at times; pain in eyes and blurred vision for eight months; occasional shooting pains in legs. Examination showed pupils large and fixed to light, left greater than right; knee jerks sluggish, ankle jerks absent.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
7/12/15	81	4+	4+ 0.4 c.c.		7/12/15 —
8/15/15	75	4+	4+ 0.4 c.c.		9/19/15 —
9/ 1/15	30	3+	4+ 0.4 c.c.	0003331000	3/ 1/16 —
10/27/15	0	2+	4+ 1.0 c.c.		3/24/16 —
11/20/15	3	2+	— 2.0 c.c.	0001221000	4/27/16 —
1/29/16	0	±	— 2.0 c.c.	1111000000	7/28/16 —

Treatment from August 2, 1915, to January 29, 1916:

2 provocative injections salvarsan.
7 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/7 to 1/5 mg.).

Results: After first intraspinal treatment patient began to show improvement; this continued steadily. He gained 25 pounds in weight, headaches, pains and depression disappeared; bladder and sexual power became improved. Patient has been working steadily since December, 1915, and feels in perfect health. Reflexes unchanged.

CASE 22. CEREBROSPINAL SYPHILIS

H., age 36. Initial lesion in 1910. When seen in December, 1916, he said that he had first noticed an inequality of pupils about 14 months ago. Two months later he complained of occasional heavy feeling in the back of head and neck; of fatigue, irritability and nervousness. On examination his pupils were found to be slightly irregular and reacting sluggishly to light. The deep reflexes were sluggish and unequal.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*		*Gold Sol*	*Serum*
12/12/16	16	3+	2+	1.0 c.c.	1123210000	12/12/16 —
2/ 7/17	15	3+	4+	2.0 c.c.		5/29/17 —
3/ 3/17	5	±	3+	2.0 c.c.	1122100000	
4/ 4/17	6	±	—	2.0 c.c.		
5/ 2/17	0	±	—	2.0 c.c.		
5/29/17	2	trace	—	2.0 c.c.		

Treatment from December 12, 1916, to May 26, 1917:

8 intravenous injections salvarsan.
8 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/5 to 1/2 mg.).
Several courses of mercury and potassium iodide.

Results: He is free from nervousness and irritability and the discomfort in his head and neck; he has much more endurance and has served as a medical officer in the United States Army.

CASE 23. CEREBROSPINAL SYPHILIS

H., age 33. Chancre and secondaries in 1905. Took mercury pills for three years. In 1909 began to feel nervous and depressed and was very sensitive; had spells of violent anger upon slight provocation. Fourteen months before had suffered from numbness in feet and left leg; occasional occipital headaches for one year. In 1915 had complete loss of sexual power; unequal irregular pupils reacting well to light; all the deep reflexes were hyperactive, more so on right side.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*		*Gold Sol*	*Serum*
3/ 9/16	35	3+	4+	0.4 c.c.	5555543000	1/19/16 ++++
4/ 5/16	13	2+	4+	0.4 c.c.		3/ 3/17 ±
6/21/16	9	3+	4+	0.4 c.c.	5555543000	7/ 3/17 ±
7/14/16	13	2+	4+	0.4 c.c.		1/23/18 —

10/ 7/16	13	3+	4+ 0.8 c.c.	5555543000	1/30/19 —
11/24/16	12	3+	4+ 0.8 c.c.		
12/30/16	7	2+	4+ 0.8 c.c.		
1/17/17	9	3+	4+ 0.8 c.c.		
2/24/17	6	2+	3+ 0.8 c.c.		
4/21/17	3	+	3+ 0.8 c.c.	1233320000	
9/12/17	3	+	2+ 0.8 c.c.		
10/ 6/17	4	±	4+ 1.0 c.c.		
12/ 5/17	4	±	± 1.0 c.c.		
2/23/18	3	±	4+ 1.5 c.c.		
4/20/18	3	±	4+ 1.5 c.c.		
5/18/18	1	trace	4+ 1.5 c.c.		
7/31/18	2	trace	4+ 1.5 c.c.		
9/ 5/18	2	trace	2+ 1.5 c.c.		
10/ 4/18	1	trace	± 1.5 c.c.		
11/16/18	3	trace	± 1.5 c.c.		
12/30/18	4	trace	± 1.5 c.c.	123321000	

Treatment from January 19, 1916, to December 26, 1918:

25 intravenous injections salvarsan.
36 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/10 to 1/2 mg.).
47 injections of mercury.

Results: Nervousness and depression have entirely gone and he says his irritability has disappeared. He no longer suffers from headaches or the numbness in his leg and feet.

Case 24. Paresis

L., age 57. Syphilis 14 years ago. When seen in April, 1917, he had had mental symptoms for 16 months. He refused examination and kept his eyes covered. There was little speech disturbance at that time although he had had difficulty two years before with tremor of the hands and had writing defect and constant facial movements. He had had delusions since the early period of his illness; was apprehensive and attempted suicide several times. He weighed 115 pounds, his normal weight being 185. Prior to his coming under observation he had had intensive intravenous treatment, two injections weekly over a long period.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
4/25/17	2	+	4+ 0.6 c.c.	544420000	6/27/17 ±
5/22/17	1	2+	4+ 0.6 c.c.		12/19/17 —
6/ 6/17	7	2+	4+ 0.6 c.c.		6/ 1/18 —
7/ 3/17	2	2+	+ 0.6 c.c.		11/ 2/18 —
8/16/17	2	+	+ 0.6 c.c.		
9/ 6/17	2	±	2+ 0.8 c.c.		
10/17/17	8	2+	2+ 0.8 c.c.	555443100	
11/ 8/17	5	+	3+ 0.8 c.c.		
12/19/17	13	+	3+ 0.8 c.c.		
2/ 6/18	5	±	4+ 0.8 c.c.		
3/ 6/18	2	+	3+ 0.8 c.c.		
4/20/18	1	±	4+ 0.8 c.c.		
6/ 1/18	3	±	± 0.8 c.c.		

7/13/18	2	trace	3+ 1.0 c.c.	1112100000
11/ 2/18	9	+	2+ 1.0 c.c.	
12/ 2/18	4	±	± 1.0 c.c.	1122100000
1/22/19	0	+	2+ 1.0 c.c.	

Treatment from April 23, 1917, to June 1, 1918:

4 intravenous injections salvarsan.
25 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/3 to 8/10 mg.).

Results: For the past year patient has shown a gradual improvement both in his mental and physical condition. He has no expansive ideas, but still has delusions at times. He converses freely and will talk for an hour or more in a perfectly rational manner. He reads the papers and the stock market quotations, takes an interest in his surroundings and will discuss business matters with his former associates who report that they can detect no mental abnormality. His memory is good for recent events. At the present time his general health is excellent; he weighs 190 pounds.

Case 25. Cerebrospinal Syphilis

S., age 37. Chancre in 1902; no secondaries. Treatment consisted of mercury by mouth for about one year. When seen in April, 1918, he gave the following history: For two years he had been nervous and irritable. His wife said he had grown very selfish, slow mentally and forgetful. He had lost all interest in his work. In February, 1917, he had a left-sided hemiplegia. After several months' treatment, mercury and potassium iodide, his paralysis disappeared. In February, 1918, he became unusually nervous and irritable and the following month began to have attacks of motor aphasia. On April 13 he was unable to speak for eight hours. On examination his deep reflexes were all found to be hyperactive and unequal. The motor power on the left side was slightly impaired. He had a right external strabismus; his pupils were unequal and irregular. The light reflexes were active.

	Cerebrospinal Fluid				
Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
4/24/18	8	2+	4+ 0.2 c.c.	2233210000	4/17/18 +++
6/ 8/18	2	2+	4+ 0.4 c.c.		1/ 4/19 —
7/13/18	3	±	4+ 0.4 c.c.		
8/10/18	3	±	3+ 0.4 c.c.		
9/21/18	3	±	+ 0.4 c.c.		
11/23/18	1	±	4+ 0.8 c.c.		
12/21/18	3	trace	3+ 0.8 c.c.		
1/29/19	3	trace	4+ 1.0 c.c.	1112100000	
3/25/19	2	trace	4+ 1.5 c.c.		
4/23/19	2	trace	4+ 2.0 c.c.		

Treatment from April 22, 1918, to January 25, 1919:

13 intravenous injections. After the first intravenous injection patient had several convulsions during the nights of April 17 and 18, each lasting about fifteen minutes.
10 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/7 to 1/2 mg.).
Several courses of mercury.

Results: Patient has been back at work for several months and states that he has not felt so well in five years. He is much more alert mentally; his memory is better and his nervousness and depression have left him. He has no more headaches, pains, bladder, rectal, or eye disturbances and no ataxia.

CASE 26. TABES DORSALIS

H., age 54. Infection 29 years ago. Treatment internally and by inunction for two years. Twelve years ago noted pains in legs. One year later retention of urine and very marked ataxia. Physical examination in January, 1917, showed Argyll Robertson pupils, absent deep reflexes and sensory changes with a marked Romberg and very ataxic gait.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
1/24/17	29	3+	4+ 0.2 c.c.	2233221000	1/27/17 ++++
2/10/17	25	3+	4+ 0.2 c.c.		9/12/17 ++++
3/24/17	13	3+	4+ 0.2 c.c.		
4/28/17	5	2+	4+ 0.2 c.c.		
6/ 9/17	6	+	4+ 0.2 c.c.	1233210000	
7/27/17	1	2+	4+ 0.2 c.c.		
9/12/17	3	2+	4+ 0.4 c.c.		
11/ 3/17	3	+	4+ 0.4 c.c.	1233210000	
1/23/18	3	+	4+ 0.4 c.c.		
3/23/18	3	trace	4+ 0.4 c.c.		
5/18/18	1	±	4+ 0.4 c.c.	1233210000	
7/13/18	2	trace	4+ 0.4 c.c.		
10/12/18	3	±	4+ 0.4 c.c.		
12/21/18	0	trace	3+ 0.4 c.c.	1122100000	

Treatment from January 24, 1917, to December 21, 1918:
13 intravenous injections salvarsan.
15 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/20 to 1/4 mg.).

Results: Very marked increase in leg pains followed both intravenous and intraspinal treatment, necessitating intervals of one month to six weeks between injections. After abatement of the reaction following treatment the patient noted some improvement in the lightning pains and in his gait. The improvement, however, was not sufficiently marked to justify the continuation of treatment.

CASE 27. PARESIS

E., age 48. Chancre of lip at age of 21. Took mercury and potassium iodide for six months. No symptoms of any kind until July, 1915, when he had a nervous breakdown. He complained of great fatigue, loss of ambition and inability to apply himself; had difficulty in thinking and reasoning properly and was very nervous and somewhat irritable. Was first seen in June, 1917, when he stated that he had suffered from constant headaches in back of head. Had had two attacks of loss of consciousness each lasting ten to fifteen minutes, also several attacks of transient aphasia; had no pains or ataxia; no bladder or sexual weakness. He talked rationally and had full insight into his condition. No speech defect; his pupils were irregular, unequal and fixed to light; deep reflexes hyperactive and equal in lower extremities, unequal in upper.

Cerebrospinal Fluid

Date	*Cells*	*Globulin*	*Wassermann*	*Gold Sol*	*Serum*
6/13/17	11	4+	4+ 0.2 c.c.	5555441000	6/15/17 +
7/14/17	28	3+	4+ 0.2 c.c.		1/16/18 +
8/ 3/17	14	3+	4+ 0.2 c.c.	5555442100	2/25/19 ++++
9/ 6/17	8	3+	4+ 0.2 c.c.		
10/20/17	4	3+	4+ 0.2 c.c.		
11/24/17	3	2+	4+ 0.2 c.c.		
12/22/17	4	2+	4+ 0.2 c.c.	5555431000	
1/19/18	3	4+	4+ 0.2 c.c.		
2/16/18	5	3+	4+ 0.2 c.c.		
3/16/18	3	4+	4+ 0.2 c.c.		
4/ 6/18	3	2+	4+ 0.4 c.c.	5555442100	
5/11/18	3	2+	4+ 0.4 c.c.		
6/22/18	4	±	4+ 0.4 c.c.		
7/27/18	2	±	4+ 0.4 c.c.		
8/22/18	3	+	4+ 0.4 c.c.		
9/21/18	4	+	4+ 0.4 c.c.		
10/23/18	3	+	4+ 0.4 c.c.		
3/ 8/19	2	+	4+ 0.4 c.c.	5555431000	

Treatment from July 9, 1917, to March 8, 1919:
30 intravenous injections salvarsan.
20 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/10 to 1/2 mg.).

Results. Has had no more attacks of unconsciousness and is less nervous and irritable. Speech has become more hesitating and evidence of mental deterioration, though slight, has been noted by his wife. Has lost to some extent his ability to determine locations and directions in motoring. Progress of his trouble has probably been retarded by treatment though no marked improvement can be noted.

CONCLUSIONS

Results following the treatment of syphilis are largely dependent on the age of the infection. For this reason the importance of early diagnosis and energetic treatment has been emphasized.

In early syphilis the spirochetes are numerous, widely disseminated, and cause little or no tissue destruction, organisms accessible to the specific drugs are destroyed and in favorable cases cures are obtained. In a large percentage of cases, however, the treatment is not carried out in an intensive fashion and as a result the organisms persist in the viscera, cardiovascular or nervous system and slowly cause tissue reactions and final degeneration.

A serologic cure in cases of syphilis in the late secondary stage and following this is difficult to obtain and requires expert knowledge in the use of our therapeutic agents.

When the central nervous system is invaded the problem is complicated by the highly organized nature of the tissues, the results of secondary degenerations and the inaccessibility of the spirochetes in certain types of neurosyphilis. In the majority of cases a strain of spirochetes invades the cerebrospinal axis before or during the treatment by drugs by the usual channels and fails to respond to continuous administration of antisyphilitic agents given in this way. The progress of the infection may be delayed by drugs assisted by the defensive forces of the body. It is seldom cured. Clinical symptoms are modified or disappear for a time but usually return unless the serology of the spinal fluid and blood become negative for a definite period. The control of the pathologic changes in the brain and cord is only possible by repeated examinations of the spinal fluid. We have no definite data as to the number of cases of neurosyphilis cured by the older methods of treatment. Frequent relapses and eventual termination in degenerations of the majority of cases so treated lead to the belief that few were cured. The need, therefore, is for a more direct method of attacking spirochetes in the central nervous system. The intensive use of salvarsan intravenously combined with mercury and potassium iodide cures a definite number of cases. All methods of treatment fail in certain types of neurosyphilis because of the inability to reach the organisms in inaccessible localities and because of secondary degenerations of tissue which can not be restored. Intraspinal treatment is successful in certain types which fail to respond to other methods or which become stationary after a definite clinical and serologic improvement.

Success or failure in the use of intraspinal therapy depends on the technic employed and the persistence of the physician in carrying it out. Above all it depends on the cytobiological indications which are present in the spinal fluid for initiating or persisting in this mode of therapy.

The order in which the various reactions disappear is indicated in the accompanying tables. The cytology is usually the first phase to be influenced in persistent infections. In some cases treatment must be continued for from one to two years before a definite impression is made on the globulin content or the Wassermann reaction. Modification in the intensity of the globulin reaction is usually followed by a weakening in the strength of the Wassermann and by a change in the gold sol reaction. Rapid changes in the Wassermann reaction when strongly positive in the high dilutions, in my experience, do not occur except in cases of early syphilitic meningitis. In old cases of neurosyphilis a gradual diminution in the intensity of the Wassermann reaction is of good prognostic import, and when it finally becomes negative, cases I have examined after one, two, and three years have shown no return of any of the previous phases.

SOME NOTES ON SYPHILIS OF THE DIGESTIVE TRACT

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BEFORE presenting in detail notes on rather unusual cases of syphilis of the digestive tract, it may be of interest to briefly review the general teaching on this subject, which, in turn, makes peculiarly striking the general belief in the rarity of luetic lesions of the digestive apparatus, a view in which we can hardly concur, in the light of our experiences in the past few years. In addition to the role played by syphilis in arteriosclerosis and the ever growing belief that gastrointestinal arteriosclerosis is a real factor in the production of both organic and functional disturbances in the gastric and intestinal spheres, we have been struck by the role syphilis may play in producing pictures very similar to those of carcinoma and ulcer on the one hand, while on the other, we have met with a number of cases of paraluetic (tabetic) manifestations in the digestive sphere apart from the well-recognized gastric and colonic crises, the former often incorrectly diagnosed as gastric or duodenal ulcer, or local peritonitis, or gallstone colic, the latter as acute appendicitis, or intestinal obstruction, or acute bacterial or toxic enterocolitis.

It is rather interesting, for example, to note that Osler in his *Text Book of Medicine* devotes only sixteen lines to the subject of gastrointestinal lues, mentioning the rare syphilitic esophageal stenosis, calling attention to the extreme rarity of syphilis of the stomach, and making no mention of its clinical aspects, speaking of the occasional ulcerations of small intestine and cecum due to this cause, while, obviously noting that the most common seat of luetic trouble in this tract is the rectum, due to the presence of gummata, which slowly breaking down, lead finally to stricture.

In fact, it is surprising how little attention is paid to syphilis of the stomach in all the standard textbooks, though somewhat more space is given to a consideration of syphilitic disease of the intestine—especially since Cruvelhier in 1854 published his monograph on the subject.

In *hereditary syphilis* it is not especially uncommon to find intestinal ulceration with diffuse infiltration of the intestinal wall, sometimes associated with gummata, often with extensive periarteritis—with diarrhea, often of the dysenteric type, as the chief symptom, and here, as in other forms of intestinal lues, often extremely difficult to diagnosticate from intestinal tuberculosis.

In *acquired syphilis* the intestinal symptoms are not well recognized except in the tertiary period—where intestinal ulcerations, often annular, and especially numerous in the rectum and terminal ileum, have been described—sometimes due to the amyloid degeneration so commonly associated with lues, sometimes to the caseation of gummata, where perforation is rare, and where, especially in the rectum, stricture may supervene. Here, again, the usual symptom is a rebellious diarrhea in the earlier stages, often with dysenteriform symptoms, tenesmus, mucus, blood and pus in the stool, and sometimes fairly profuse hemorrhages—although if stricture follows, constipation is the rule, sometimes alternating with diarrhea. The diarrhea met with sometimes in the secondary stage is more likely to be due to the therapy employed, especially the mercury, although sometimes it is definitely referable to the disease itself—which occasionally manifests itself in a true typhoid state, associated with diarrhea.

Although not strictly falling within the scope of this article, mention should be made of the buccopharyngeal signs and symptoms of syphilis, especially of its primary and secondary stages, the various forms of extragenital chancres, labial, lingual, etc., often being a source of considerable diagnostic difficulty on the part of the gastroenterologist in whose sphere lesions of lips and tongue and pharynx rightly belong; and it is to him, also, that another form of extragenital chancre, that of the rectum, is often brought for diagnosis. In the secondary stage very striking and very various manifestations are to be met with, such as various forms of stomatitis, especially the erythematous, and syphilitic anginas, although, of course, the mucous patches, not, however, always of characteristic or classical form, are by far the commonest and best recognized lesions in this locality.

Of *tertiary lesions* of mouth and pharynx—one should mention the *syphiloma* of the lips, involving sometimes the lower lip only, sometimes both lips; the *sclerotic glossitis* of luetic origin, frequently associated with *gummatous glossitis,* sometimes leading to ulceration, and various somewhat similar lesions, sclerotic or gummatous or ulcer of *palate, pharynx* and *tonsils,* while possibly some cases of buccal and lingual leucoplakia may be syphilitic in origin.

In passing, because of their intimate relationship to stomach and intestine, one should mention the various luetic diseases of the *liver* and of the *pancreas.*

In the case of the *liver* we may find in the congenital form a diffuse hepatitis which may be delayed in its manifestations, while in acquired syphilis the liver is not often involved in the secondary stage, though jaundice, probably part of a general syphilitic hepatitis, is occasionally met with.

The *tertiary* lesions of the liver, of course, are well known, manifesting themselves as they do in the form of gummata, or scar, or sclerosis, the last usually combined with gummata and the symptoms being those of the ordinary cirrhosis of the liver, occasionally of the biliary cirrhosis, while the symptoms of gumma are practically those of tumor of the liver, especially cancer. We see so many cases of gumma of the liver, previously diagnosticated carcinoma, that it is our practice, in the case of every liver tumor, even in the absence of a positive Wassermann reaction, to try the effect of mercury and the iodides before making a final diagnosis.

In the case of the *pancreas,* we may meet with *congenital syphilitic pancreatitis,* to which especial attention was first called by Birch-Hirschfeld in 1880, who found it in thirteen of twenty-three cases in children with congenital syphilitis, a considerably higher instance than in series subsequently reported.

In *acquired syphilis* the pancreas may be the seat of gummata, or of syphilitic induration, somewhat similar to the changes met with in the liver, and in either case, notably the former, an aftermath may be found in *pancreatic scars.* Whether syphilis plays any considerable role in the etiology of *chronic interstitial pancreatitis* is open to doubt, and Opie, who has noted evidence of lues in only one of thirty cases of this condition, thinks that the etiologic relationship of syphilis to a diffusely distributed inflammation of this organ is doubtful.

We wish to call attention to a series of luetic cases presenting the various digestive groups of symptoms in their entirety in each of which groups we have had a number of cases. They may be classified as follows:

I. Those simulating carcinoma—with palpable tumor mass.

II. Cases with symptoms indicative of the ulcerative types, i.e., erosions, gastic or duodenal ulcer.

III. The indefinite cases, showing fullness, distress, pain, etc., definitely digestive, but not dependent on food take—indicative of appendix—gall-bladder involvement, chronic catarrhal gastritis.

IV. Nausea and vomiting, or diarrhea.

I. *Those Simulating Carcinoma—With Palpable Tumor Mass.*—The history of the case may or may not be of interest—the patient had possibly been careless in his habits or not as the case might be—premonitory symptoms of fullness and distress, eructations and indefinite discomfort are at times complained of, and this cycle of events has continued for a longer or shorter length of time when the patient begins to note a pain dependent or independent of the intake and character of food; eructations are noted with no relief, or at times temporary subsidence of marked fullness or time pain. Heartburn at times is noted, as is also nausea, and if the tumor mass is at the pyloric end, we find vomiting as a striking symptom. Hematemesis is rarely present, while melena, in the great majority of cases, is absent, although if the tumor mass ulcerates, blood (occult blood, at least) is noted. The appetite is variable, but in those where stenosis of the pylorus is beginning or has become marked, thus causing a blocking of the outlet with stagnation and fermentation of food, the unfortunate and disagreeable, as well as serious complication, true anorexia almost invariably appears.

The bowels are mostly constipated, notably in the obstructive types.

The general appearance is suggestive of malignancy because of the marked emaciation due to diminished intake of food—a cachexia in these cases may also be noted.

A very important point, and one well worth bringing to the front, is the question of age. Here we often find the person far under the commonly accepted age limit supposedly indicative of carcinoma. The family and personal histories are mostly of no moment, excepting the latter which, of course, may bring out the nature and time of infection. However, a certain number are not aware in the slightest degree of syphilitic invasion—a positive Wassermann being their first intimation that this disease is present. The gastric examination varies greatly, pointing at times to obstruction, or free passage, depending, of course, upon the location of the tumor mass; the acidity is of the widest range, going from a true achylia to hyperacidity. The urine shows nothing of special significance. The x-ray may simulate carcinoma, but in the majority of cases there is not the clear-cut filling defect one meets with in malignant tumors of such an advanced stage. We have noted at times a fuzzy appearance where the tumor may be located on either curvature, however, in most instances the edges were not obliterated. As in carcinoma, pyorrhea and deficient teeth are often noted. With the marked emaciation found in advanced cases, dyspeptic symptoms, filthy mouth conditions, varied gastric findings, tumors causing stenotic processes, and occasionally suggestive x-ray findings, one, indeed, is unable at first to definitely state that the case is not one of carcinoma.

We have always been admonished to view with suspicion persistent digestive symptoms after forty—relative to carcinoma—and from the experience we have gained in digestive pathology of luetic origin, it would be wise to look askance at obscure, indefinite and persistent digestive complaints at any age which are prone to be unresponsive to treatment, and where malignancy can be excluded.

II. *Cases Indicative of Ulcerative Types.*—This is a most interesting class as we are many times able to elicit a history of indiscretion in diet resulting in indefinite and vague abdominal discomforts, followed by distinct fullness and distress, which is dependent upon food intake. Later pain is noted, its types are varied, sharp, shooting, cramp-like, boring, burning, etc. Heavy foods most often intensify while the seasons, posture, exercise, and mode of onset parallel exactly those complaints we know to be symptomatic of ulcerative processes involving the stomach and duodenum. Eructations are met with—bitter, sour or tasteless—at times rendering temporary relief. Nausea is rather a common symptom, while vomiting occurs mostly after the onset of true obstruction, pyloric or cardiac. Hematemesis does occur, but not as frequently as in other ulcers. Melena is found quite often, depending, of course, upon the degree of ulceration. The appetite may remain good until the pains become severe or the grade of obstruction marked. The bowels are variable with a tendency to constipation, while the weight most markedly declines. Regarding the gastric findings there is nothing pathognomonic relative to fasting stomach or test breakfast. In obstructive cases the same characteristics mark the stagnant content as in nonluetic or malignant processes. The x-ray investigations many times show pylorospasm, gastrospasm, etc., similar to the various irritative lesions in these parts. The fact that this symptom-complex is probably of luetic infection is shown by its quick response to specific treatment.

III. Indefinite Group.—Here we usually meet with digestive complaints of long standing and varied in character, the onset often insidious and slowly progressive—vague abdominal discomfort, at times related to food intake, and quite as often bearing no relation to diet. Fullness and distress are noted in many cases, as is also pain, the latter of no special type, neither is it confined to a definite location, one time appearing at the appendix, another in the gall-bladder region, then again in the epigastrium, under the left costal margin, etc., thus giving us a vague digestive picture, without a true ulcer, appendix or gall-bladder syndrome, in each of which groups we have had a number of cases.

No discussion of luetic manifestations of the gastrointestinal tract would be complete without calling attention to the very interesting conditions met with in this sphere in paraluetic diseases, notably in tabes dorsalis. Gastric crises which may simulate acute gall bladder attacks or even high intestinal obstruction or perforation and colonic crises which are frequently regarded as atypical cases of acute appendicitis or intestinal obstruction, are too well known to be discussed here in detail. We wish, however, to call attention to certain other gastrointestinal symptoms of tabes which are not so well known, but are of equal interest in this connection.

IV. Nausea and Vomiting.—This forms a small but important group, and we have been much interested in following closely some cases which fall in this category. These patients enjoy longer or shorter periods of absolute immunity during which no digestive symptoms present themselves. Following this period of freedom, a marked outbreak of distressing and persistent nausea and vomiting is noted. In some cases the nervous system seems to play a not unimportant role in the precipitation of attacks, and one must be alert lest the patient with a psychoneurotic taint is completely misjudged when this malady asserts itself. We have noted this nausea-vomiting symptom-complex brought about in the psychoneurotic after marked mental or physical exertion, or a combination of both. The manifestations are outspoken; the nervous symptoms decided for a day or so, general malaise, anorexia, tendency to insomnia, slight nausea; then after a period of twenty-four to forty-eight hours, active nausea and great distress followed by violent vomiting and retching—this latter may continue for several days (5 to 7 or more), and is markedly resistant to medication of every description, in consequence of which the patient becomes weak, debilitated, exhausted and loses much weight. The material vomited is changeable in general characteristics, but in most instances is of a bilious nature (yellow or dark green). There is a gradual diminution in all of the above-mentioned symptoms until the normal condition of the patient is again reached.

One can easily see from the described syndrome how easy it might be to ascribe this symptomatology in a psychoneurotic to a purely functional disorder of the nervous system.. After careful and painstaking study of these cases we are convinced of their close relationship to the true gastric crises so well known to every one, but in many instances overlooked when not presenting themselves according to textbook description. Another most interesting type relative to the group presenting active vomiting manifestations is that where excessive amounts of pure mucus are secreted and evacuated. Along with this one will note that other membranes besides those of the stomach are prone to overactivity, notably the nasal lining. In these cases we have periods of decided remittence, but not absolute intermittence as in the nausea and vomiting group just outlined. The membranes are in a constant state of irritability responding to the slightest stimulus. Intake of food, no matter of what character, will often inaugurate an enormous flow of thick, viscid mucus, the amount being so great that the stomach is forced to eject it. Along with this disagreeable procedure we note distressing salivation and excessive nasal secretions, the patient with red nose, stuffed nasal passages, suffused eyes and general discomfort, presenting a picture quite analogous to hay fever.

In addition to the above, irregularity of bowel movement is noted—at one time diarrhea, at another constipation, the greater number leaning toward the former which one would expect because of the hypersecretory nature of the ailment. Because of the disagreeable results of eating it is but natural that true anorexia may ensue followed by emaciation and general asthenia, unless the process is checked—a feat not easy of accomplishment. Fullness, distress, eructation, in fact, general dyspeptic symptoms in great variety, almost invariably add themselves to the already enumerated multiplicity of truly disagreeable and debilitating complaints.

The above facts may be useful to remember when we are brought in to consult with cases of very active gastromyxorrhea.

Periodic Attacks of an Intractable Diarrhea in Tabes.—We have met with three cases of tabes dorsalis, with absolutely typical findings, Argyll Robertson pupil, absent knee jerks, Romberg sign, and previous luetic history, in which instead of the colonic crises (an intestinal analogue of the better known and much more frequently met with gastric crises) we found periodic attacks of severe diarrhea. As the most thorough investigations of the gastric contents, stool studies, neurologic analysis, and thorough examination of all the organs and secretions failed to show any cause for the condition, we were obliged to assume that it represented one of the unusual intestinal symptoms of the tabes itself. We regarded these cases as probably truly neurogenic, representing either overstimulation of vagi, or inhibition of splanchnics, and considered them as motor equivalents, as it were, of the well-recognized colonic crises met with in this disease.

CONCLUSION

We feel that we have shown in this presentation of cases studied by us with great care during the past few years that syphilis plays a very much more important role in gastrointestinal pathology than is usually supposed. When one realizes, as we have shown, that carcinoma or ulcer of the stomach, various functional or organic dyspepsias may be absolutely duplicated by lues of the stomach, while the paraluetic tabes may present the most variable gastrointestinal syndromes; here violent epigastric pain, suggesting perforating ulcer or gallstone colic—here intractable nausea and vomiting—here colonic crises, which almost exactly duplicate in symptomatology either acute appendicitis or acute enterocolitis, while in other cases periodic attacks of the most profound diarrhea may be met with—it should make us realize that we should always be on the alert for manifestations of this disease either in the past history, or in the complete physical examination of the patient. We feel sure that if such possibilities are thought of, if the history is taken carefully, if the physical examination is complete, with, of course, careful study of blood or even of spinal fluid, if indicated—that an increasing number of gastrointestinal lesions regarded as due to other causes, will, in reality, be shown to be syphilitic in origin.

SYPHILIS IN THE NEGRO*

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INTRODUCTION

IN considering the subject of syphilis in the negro one is immediately impressed with the paucity of literature dealing with this most important problem. And not only have we been able to find in a search of the literature comparatively few articles dealing with the subject, but a great percentage of the articles we have found deal in a large measure with generalities instead of specific facts.

Among the earlier references to syphilis in the colored race may be mentioned Taylor's[1] article on the peculiarity of the papular syphilide in the negro, published in 1873; Atkinson's[2] paper on early syphilis in the negro, published in 1877; Barthelemy's[3] article on syphilis in a negress, published in 1881; and the paper by Dixon[4] published in 1879 which deals with the differences of syphilis in the negro and in the white.

In recent years a few very valuable contributions to certain phases of the subject have been published and will be referred to later.

The present study of syphilis in the negro is based upon the experience of one of us in dealing with syphilis in the South, and upon the intensive study of 300 consecutive cases of syphilis occurring in negro soldiers in the Venereal Service of Camp Dodge.

ORIGIN OF SYPHILIS IN THE NEGRO

One of the first problems which attracts interest in dealing with syphilis in the negro is that of its origin. We refer now particularly to syphilis in the American negro, and the question is, did the American negro contract the disease before or after being transported in slavery to this country.

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Barthelemy[3] quotes Alibert as saying that the negroes from Africa spread this plague in the New World. Bloch[5] cites Leo Africanus and says that this writer states syphilis was unknown in Northern Africa until 1520 when it was introduced from Europe. Bloch also states that Antonius Gallus said in 1540 that there was syphilis in Africa. From this Bloch contends that the Portuguese carried this disease to all the coast regions of Africa.

Inasmuch as the first slaves were landed in America in 1619 it would seem that some of the syphilis in the American negro is the result of the contraction of the disease before the negro was transported. Of course it must be understood that syphilis has been from the earliest days of slavery, and is still being, transmitted from the white race to the negro, and we might add, from the negro to the white race.

PREVALENCE OF SYPHILIS IN THE NEGRO

There has been a great deal written and spoken in a general way concerning the prevalence of syphilis in the negro, and there is a practical unanimity of opinion that this disease is far more common in the colored race than in the white. However, there has been done comparatively little work of a scientific character to determine the exact incidence of syphilis in the negro.

Jones,[6] after an experience of more than six years in a large clinic composed almost entirely of negroes, believes that he is justified in making the statement that 75 per cent of that class of negroes who come as patients are syphilitic.

Quillian[7] states that he believes that 60 to 70 per cent of negroes have syphilis.

Murrell[8] believes that another fifty years will find an unsyphilitic negro a freak, unless some such procedure as vaccination comes to the relief of the race, and that in the hands of a compelling law.

Fox[9] collected statistics of 2,200 cases of skin disease among negroes and found 27 per cent were syphilis, while of 32,000 cases of general disease among negroes 5.82 per cent were lues.

Hazen[10] in a similar study of 2,000 cases of skin disease found 22 per cent syphilis, and of 90,172 cases of general disease 5.37 per cent syphilis.

Baetz[11] states that of 8,226 adult male medical cases in colored canal laborers there were 500 cases of syphilis, or about 6 per cent.

Lynch[12] and his co-workers conclude that from 50 to 60 per cent of the major class of negroes are infected.

Hindman[13] in a study of syphilis among insane negroes found 16 per cent of all negro admissions were syphilitic, while Wender[14] found in 106 insane negroes 53 or 50 per cent were syphilitic.

Jamison[15] states that of 1,000 medical cases in the female negro 166, or 16.6 per cent were syphilis.

Bayon,[16] dealing with syphilis in the African native tribes and among the native workers on the Rand, found that about 5 per cent of those he calls "raw" or "pagan" natives had clinically recognizable syphilis, while 33 per cent of the semicivilized, or those who work for white men, are syphilitic.

McNeil,[17] after a Wassermann survey of 672 negroes, including 200 apparently healthy adults, the remainder being clinic cases, feels that he may draw the conclusions that between 25 and 30 per cent of apparently healthy adult negroes of Galveston are syphilitic, while the incidence of syphilis among sick negroes is between 40 and 50 per cent.

We have been unable to determine the exact incidence of syphilis among the negro troops of Camp Dodge, no attempt being made to perform Wassermann tests on all men. Of the 16,212 negroes who have been in camp only 300 have been under treatment for syphilis. This is not quite 2 per cent, but by no means represents the total incidence of the disease as only such cases were treated as had clinical lues with recognizable lesions.

ETIOLOGY

Of course syphilis in the negro is due to the Spirochete pallida as in syphilis in other races, but there are certain secondary etiologic factors which must be considered.

1. *Idiosyncrasy—Immunity.*—That the negro is any more or less susceptible to syphilis than other races is questionable, but that there may be certain individuals who are less susceptible to infectious diseases in general and to syphilis in particular, is undoubted. However, it is not believed that the lessened susceptibility is due to the presence of specific antibodies, but is due to an inherited resistance and absence of debilitating conditions.

If we admit the theory that there must be a break in the continuity of the integument for the spirochetes to gain entrance to the body, it is possible that the negro's well-known sexual impetuosity may account for more abrasions of the integument of the sexual organs, and therefore more frequent infections than are found in the white race.

2. *Age.*—No age is free from, nor proof against syphilis, but in the negro syphilis is contracted on an average at a younger period of life than in the white race. Quillian[7] states that he has never examined a negress over fourteen years of age who was a virgin, and our own observations support the oft-repeated statement that the negro begins his sexual activity at an early age. And not only does he begin his sexual activity at an early age, but occasionally at least, he contracts syphilis considerably before puberty, as one of us has seen a chancre of the penis in a negro boy of six years who said he had had intercourse with his sister.

3. *Sex.*—One of us[18] has written the following: "That syphilis should be more common in men than in women is almost self-evident. The social law which throws a cloak about the chastity of women in the home and permits with little or nothing more than a shrug the 'sowing of wild oats' by men is in itself enough to cause the number of syphilitic men to exceed the number of women contracting the disease."

That this social law applies to the women of the colored race as a whole is at least doubtful. The statement of Quillian[7] quoted above, that he had never examined a virgin negress over fourteen years of age, would seem to imply that the women of the race indulge in sexual intercourse as much as the men, and it would naturally follow that they contract syphilis as frequently. In fact Lynch[12] and his coworkers state that negro women are more often infected than men.

4. *Civil State.*—In the white race it is evident that among men the unmarried are more frequently exposed to syphilitic infection than the married, and that among women the reverse is true, since a large percentage of white women contracting syphilis do so from their husbands. But from the well-known looseness of the morals of negroes, permitting more or less promiscuous sexual intercourse regardless of marriage or lack of it, it would seem that the civil state would have little or no bearing on the subject.

5. *Social Condition.*—In the antibellum days the negro was a slave and as such he was a valuable piece of property, so it behooved

the slave owner to take the very best care of his property possible. Therefore before the Civil War there was comparatively little syphilis among the negroes. However, when the protecting care of the master was withdrawn from the negro and he was thrown upon his own resources his social condition in many instances became deplorable. The conditions of housing were, and in many sections still are, unthinkably poor. Very often we have seen as many as ten or twelve adults sleeping in a single small room. This certainly tends to promiscuous intercourse and the spread of venereal disease.

Then, too, the negro on account of his low social condition is usually uncleanly in his habits and does not employ even the crudest prophylactic measures.

CLINICAL MANIFESTATIONS AND PATHOLOGY

While the long-established immutable laws of evolution characterizing the epochs of luetic infection must, of a necessity, obtain in every race, it seems only fair to assume that certain of these characteristics may vary with the racial host in which infection takes place. The specific cause and peculiar pathology can not vary, yet they may result in clinical manifestations, whose type and characteristics are the results of racial vulnerability or peculiarity of make up. At least, it seems a noteworthy fact that colored luetics present a peculiarity of type, or a greater frequency of certain types, than that usually found in whites. This has been the experience of other observers, as with ourselves, and some of these observations have seemed worthy of mention in the following paragraphs. Not only is one's attention directed to this racial peculiarity of lesional types, but also to the virulence of the infection itself, as influencing symptoms.

1. *Chancre.*—Twenty per cent of the cases of the present series have been patients with chancres, varying in duration from a few days to several months. In the main they have presented no peculiar characteristics nor difficulty of diagnosis. It is only natural to expect, if we consider the average hygienic ideals of this class of patients that mixed lesions are of greater frequency, and this our observations have borne out.

The striking characteristic, and one which we may attribute to many cutaneous syphilides in the colored race, is that of indolence. In a great majority of cases of chancre the history of first appearance dated far more remotely than is our usual experience with similar

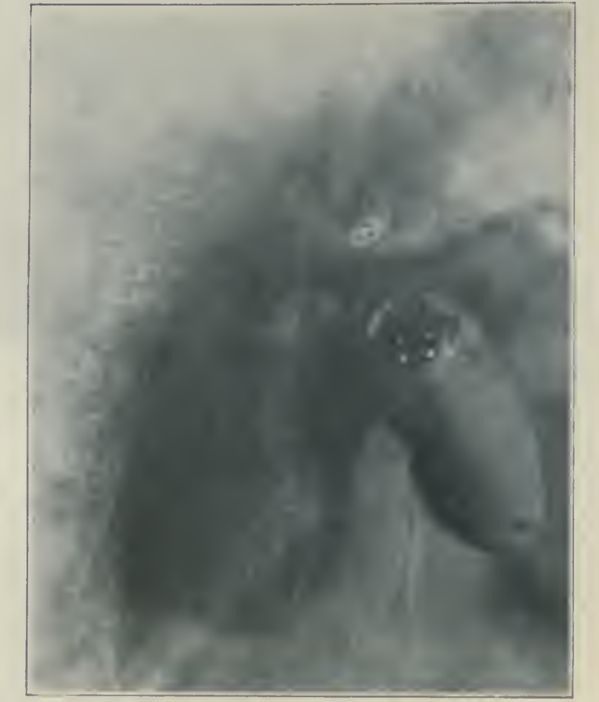

Fig. 1.—Large Hunterian chancre of penis.

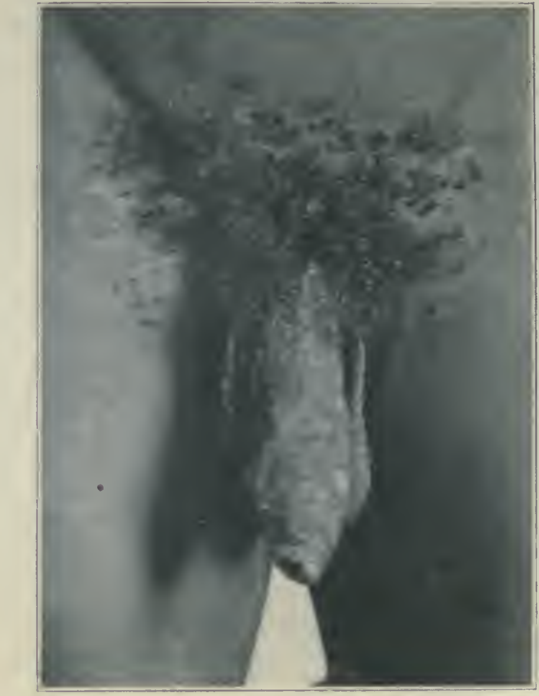

Fig. 2.—Papular (miliary) syphilides of penis. (The lesions shown were practically the only ones present on the body.

lesions in the white race. This we believe is partially explained by the fact that during the period of sexual activity the average negro has a succession of penile lesions. Consequently the history obtained varies from one month to a number of years, and while the latter is obviously incorrect, one can not help being impressed, after seeing repeated cases, that indolence is a characteristic to be emphasized far more in this type of syphilitic.

We have been impressed by the fact, which has been observed by Hazen[19] and others, that extragenital chancres are extremely rare in the colored race. Neither in the present study nor in our previous experience have we seen such lesions, nor have we obtained history of them. It is difficult to account for this, especially in view of the fact, which we shall elaborate on later, that lesions of the mucous membranes of the mouth are quite common.

2. *Skin Lesions.*—The cutaneous manifestations of syphilis in the negro includes the many lesional types and polymorphism which characterizes it in other races, yet there is a very evident preponderance of lesions of certain types, which are observed only occasionally elsewhere. This refers more especially to the so-called secondary eruptions, as our observations have been chiefly confined to patients whose age precluded any large incidence of the later lesions. In the so-called tertiary cases coming to us we have found the lesions similar in every way to those occurring in other races.

There has been some disagreement as to the frequency of the roseola in the negro, and the recorded infrequency in some instances has been explained by the lack of accurate observation. In this we are compelled to agree with Hazen's[19] statement that "macular and maculopapular eruptions are not common in the negro." In spite of most painstaking examination and giving due consideration to the difficulties from pigmentation, we have been able to diagnose but few roseolar eruptions. When present they are fairly easily recognized, occurring with the usual distribution, showing in some as macules of deeper hue or increased pigmentation, and in the mulatto standing out fully as conspicuously as in the white.

It has seemed to us that the annular lesion of early syphilis is one of the most striking, and in point of incidence, both absolute and relative, may almost be said to be peculiar to the colored race. Hazen[20] and Fox[21] particularly have devoted much study to these interesting lesions. As a result of the former's studies we have these lesions classified into several types according to origin; first, those resulting from annular arrangement or peripheral extension of primarily follicular lesions; second, those resulting from central involution or peripheral extension of small papular lesions or the annular arrangement of such lesions; and third, the central involution of a large flat papulosquamous lesion. With one or two exceptions our observations have conformed to the above. Some of the cases have apparently resulted from the circular arrangement of papular lesions, and some have likewise seemed the result of central involution of large scaly papules. On the other hand, we have not been able to satisfy ourselves that the annular eruption ever results from the confluence of follicular lesions. Furthermore, a large percentage of the annular lesions that have come to us have seemed to be of their particular configuration *per se* and not as the result of developmental changes in preexisting lesions of another type.

The lesions, as the term implies, are regular in outline, discrete, sharply defined and indurated. They vary in size from a few millimeters in diameter to the size of a quarter or larger. The lesion proper is definitely raised from the surrounding integument; often presents a white scale, and incloses an area of apparently normal skin, which occasionally shows some increase in pigmentation. Rarely the lesions are arranged in spirals or concentric rings. The favorite sites of distribution in our experience have been the face, more especially occurring on the forehead, chin, about the alae, and occasionally on the neck and trunk. As a whole they present little or no difficulty of diagnosis.

Opportunity has not been afforded for microscopical study of these lesions in the present series, but such investigation by others has revealed some interesting findings. Unna maintains that they are a result of a paresis of the blood vessels, induced by a syphilitic affection of the vascular nervous system, and that they differ from other syphilides in the absence of plasma cells and of giant cells, as well as in their form, duration and resistance to treatment.

Hazen[20] in a very able manner describes the changes as follows: "Although the infiltration around the blood vessels is considerable, it is not nearly so massive as is usual in the commoner type of papules. However, the cells are nearly all plasma cells, especially in the older parts of the lesion. At the raised rim, both the horny layer and the rete are distinctly thickened, the intrapapillary processes are elongated

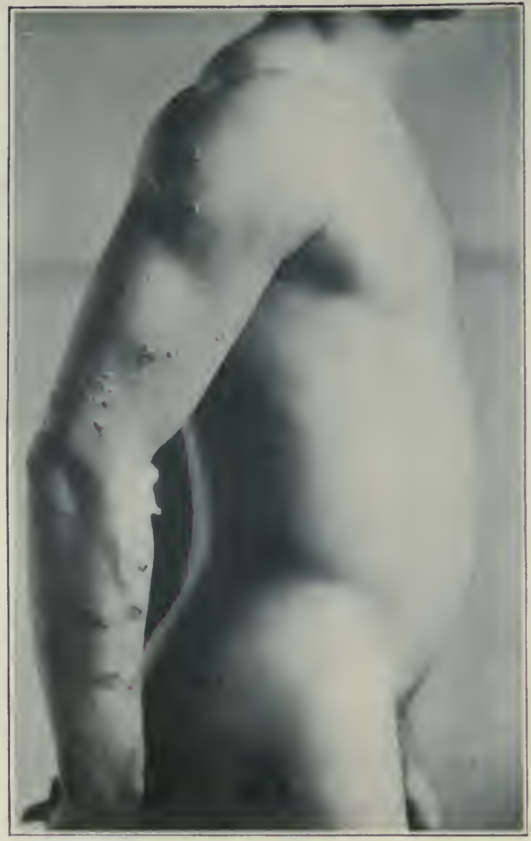

Fig. 3.—Papular syphilides of arm. Showing slight tendency to circinate formation.

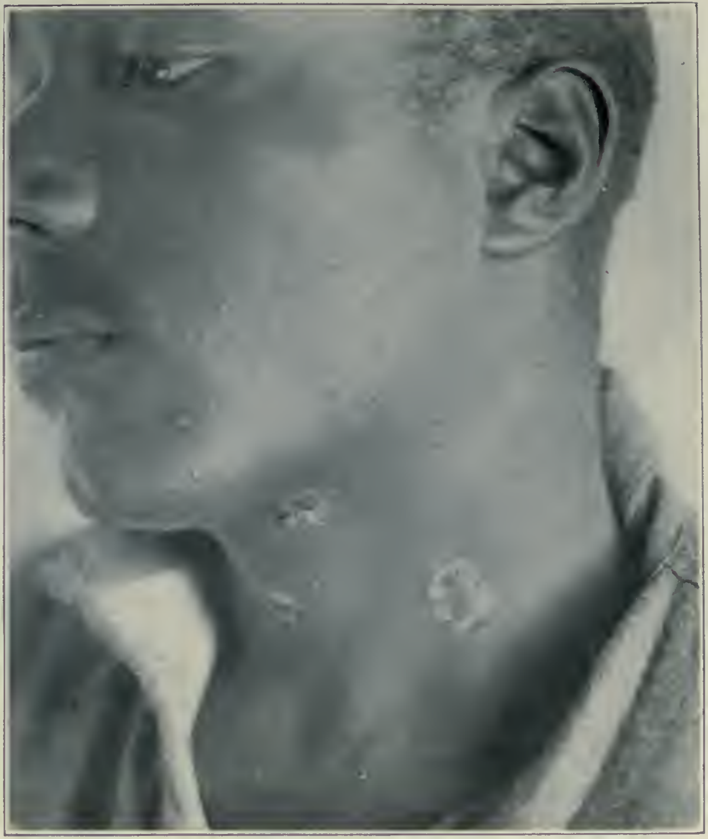

Fig. 4.—Annular papular syphilides of neck. The lesions on the face are acne.

and there is a marked diminution of the pigment of the basal layer. The blood vessels and the lymphatics of the corium and papillæ are dilated, and especially in the papillæ, there is a marked infiltration of lymphoid and fixed tissue cells with a few polymorphonuclear leucocytes and plasma cells. The whole rete, and especially the basal layer, is invaded by the types of cell just mentioned, and the basal layer will not take stains well. In the central portion the most striking features are the comparative absence of pigment, and the number of plasma cells around the blood vessels, although the infiltration is not so marked as in most cases of syphilis.''

In brief then, not only has the peculiarity of form been emphasized, but likewise has the longevity of these lesions been impressed upon us, and we can not but feel that with these, as with the chancre, and perhaps the infection as a whole, the indolence of this disease in the negro, is a peculiarity of which we are constantly reminded.

3. *Mucous Membrane Lesions.*—Involvement of the mucous membrane has impressed us as being more common in the negro. While the lesions have been of greater frequency, they do not differ in degree from those occurring in whites, unless it be in the frequently observed hypertrophic tendencies. In many of our cases, instead of being simple discrete, painful, erosive or papuloerosive lesions, they had taken on a distinct hpertrophic appearance. They have frequently presented as markedly raised papular lesions, occurring particularly on the inner surfaces of the lips and lasting over long periods of time. In fact they have frequently resembled flat condylomata, and the explanation which immediately suggests itself is the question of buccal hygiene.

4. *Condyloma Lata.*—Broad condylomata occur apparently somewhat more frequently in the negro, but differ in no way from those occurring in the white. Many cases have come to us presenting numerous flat, discrete, semieroded, papular lesions, involving the scrotal and perineal regions. Again we believe the question of personal hygiene plays an important role.

5. *Adenitis.*—The superficial lymph glands in the negro do not offer as great an aid in the diagnosis of syphilis as is the case with the white race. While in the latter a general shotty lymphadenitis is considered a part of the general picture and is confirmatory evidence of some weight, it is so frequently found in the nonsyphilized negro, as to be of doubtful value in diagnosis. With but few ex-

ceptions every negro coming to us with venereal disease of any kind has presented a general adenitis of some degree.

The splenic enlargement we believe to be of about the same frequency as in whites. The percentage of our cases showing a palpable spleen was 37. A factor to be considered in this connection, however, is the prevalence of malaria in the southern negro, and of this we have taken proper notice.

6. *Appendages.*—Involvement of the appendages apparently occurs with about equal frequency in both races. Several cases of specific alopecia have come to us, and they presented the characteristic patchy, moth-eaten appearance, easy of diagnosis and in no way differing from this condition in the white race.

Onychia and paronychia occur in the negro and differ in no respect from these conditions in the white.

7. *Osseous Lesions.*—There seems to be a general consensus of opinion that the osseous system of the negro is more frequently involved than that of other races. Especially has this been true in the experience of Carson[22] and Baetz,[11] the latter having found 60 per cent of the cases coming to him showing such involvement. In our observations the percentages of osseous lesions have not been this great, in fact, in our entire series we have seen but one case of perforated septum and only three of early involvement of the clavicle, while other osseous lesions have not been demonstrable. This discrepancy may be accounted for by the fact that our cases were made up of young individuals in whom one would expect to find only the secondary type of lesion if at all, and as many of our cases had had at least a small amount of treatment before coming into our hands these early types of involvement were not observed.

8. *Visceral Involvement.*—The circulatory, respiratory, gastrointestinal and genitourinary systems, outside of the chancre, insofar as we have been able to tell, have not been the seat of syphilitic lesions. Baetz[11] in his analysis of 500 consecutive cases, found 10 per cent showing cardiovascular lesions, and 5 per cent showing late visceral lesions. The average age of our patients apparently precluded visceral findings in any of the cases.

9. *Central Nervous System Involvement.*—Opinion is divided regarding the frequency of central nervous system lues in the negro.

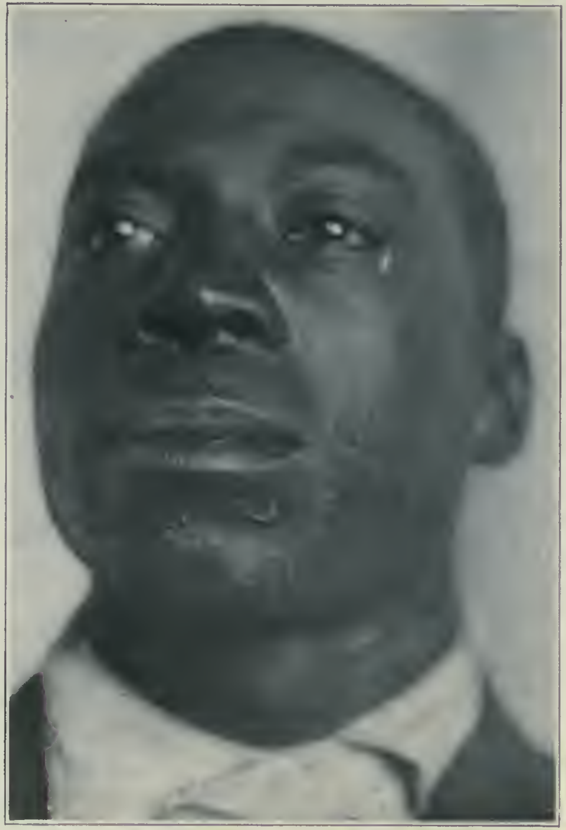

Fig. 5.—Papular syphilides of face showing tendency to circinate formation.

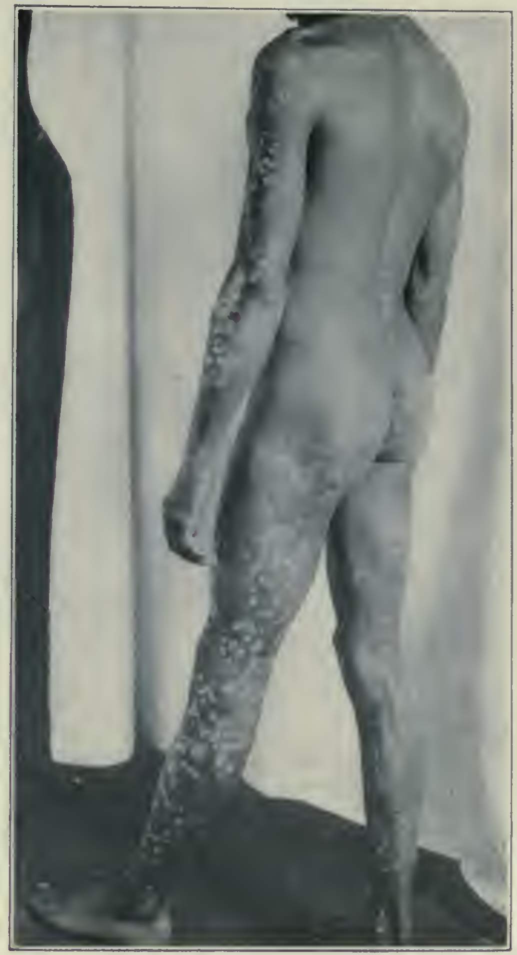

Fig. 6.—Extensive papular eruption. Many lesions show circinate formation.

Hindman,[13] writing on syphilis among insane negroes, states that 4.9 per cent of such admitted to the hospitals for the insane in the United States, were cases of general paresis, as compared with 6.6 per cent of whites admitted during the same year.

Wender,[14] in 106 cases of insanity in the negro, found 11 cases showing cerebrospinal lues, and 21 diagnosed as general paresis.

Jamison,[15] in 166 cases of syphilis in colored females, found 2 cases of tabes and 1 of general paresis.

Baetz,[11] in 500 cases of syphilis in colored canal laborers, saw no cases of tabes and only 1 of paresis, but he found 130 with abnormal knee jerks, 12 with cranial nerve palsies, and 7 with staggering gait and ataxia.

In more recent studies Hazen[10] states that the experience at the Johns Hopkins Hospital shows central nervous system involvement equally common in the two races, while tabes is less common in the colored.

Types of central nervous system involvement, other than tabes and paresis, according to Fox,[9] are more common in the negro than in the white.

Our facilities have not permitted an extensive study of the central nervous system, and in no case have we had the opportunity of examining the spinal fluid. In none of our cases has a diagnosis of tabes or general paresis been possible, and the number of patients presenting signs, either objective or subjective, of earlier involvement has been comparatively small.

CONGENITAL SYPHILIS IN THE NEGRO

Little has been written on the subject of congenital syphilis in the colored race. Carson [22] states that congenital syphilis is frequent in the negro, but that it is seen only in babies. He explains the absence of congenital syphilis in the adult by stating that syphilitic babies do not survive, and says that he has never seen Hutchinson's teeth in a grown negro.

McNeil[17] found that 9.5 per cent of negro children presented for treatment in his clinic gave positive Wassermann reactions. He concludes that "the majority of cases of syphilis among the negroes are of the acquired type, nature, fortunately, taking care of these patients with inherited syphilis by affording them an easy death, either before or immediately after birth, as well as by rendering the parents sterile.''

With these observations we are in complete accord. In the present study we have observed no symptoms of congenital lues, while in our previous experience the inherited type of the disease has rarely been encountered.

DIAGNOSIS

The diagnosis of syphilis in the negro naturally is similar to the diagnosis of this disease in other races. There are, however, certain factors which need be considered in the former which, usually at least, need not be considered in the latter.

In regard to the chancre the diagnosis is attended with no unusual difficulty, and of course depends upon the recognition of one or several of the unvarying characteristics, i. e., the induration, circumscription, satellite bubo, etc. So many of our patients have given histories of unusual duration that we are inclined to believe that spontaneous involution of this lesion occurs much later in the colored race.

Inasmuch as the circinate or annular syphilide is much more frequent in the negro than in other races it may be well to point out the conditions it resembles and from which it must be differentiated.

This type of lesion may be mistaken for *erythema multiforme*, which, however, is of more sudden onset, does not show the whitish appearance, sometimes seen in the syphilitic lesion, is most frequently found on the hands and forearms and is accompanied by more or less pruritus.

The circinate syphilide may also be mistaken for *psoriasis*, but the scaling in the latter disease is more severe, it is seldom seen on the face, and never when not found elsewhere, while slight bleeding occurs upon the removal of a scale, which does not occur in syphilis.

Tinea circinata should present no difficulty of differentiation, as it is of slower development than the annular syphilide, the edge is less indurated and more inflammatory, while the causative organism can usually be demonstrated.

The diagnostic features of the involvement of the superficial lymph glands have been discussed above.

The laboratory diagnosis of syphilis in the negro is the same as in other races; the finding of the Spirochete pallida being conclusive, and the Wassermann test constituting one of the most reliable symptoms.

PROGNOSIS

The prognosis of syphilis in the negro depends upon a number of factors, although writers vary in regard to their opinions concerning the prognosis of lues in this race.

For example, Dixon[4] wrote in 1879 that the disease yields more quickly to treatment in the negro than in the white.

Bryce[23] expressed the naive opinion that the negro sweats the disease out, that the white is usually overtreated and therefore the former usually shows less effect of the disease than the latter.

Carson[22] believes that syphilis is much more virulent in the negro than in the white. This he thinks may possibly be due to differences in reaction of the negro organism to the germ of syphilis, but more probably is due to the negro's carelessness and indifference to treatment.

Murrell[8] states that all phases of syphilis in the negro are more intense than in the white.

Hazen[10] says that he does not agree with the usual statement that the lesions of syphilis are less severe in the negro; that he can see no difference in the course of the disease in the two races, either with respect to the clinical symptoms or to the Wassermann reaction.

With Hazen's view we are in accord, although, as pointed out above, certain lesions in the negro, particularly the chancre, do show a greater indolence than in the white.

However, the chances for ultimate recovery in the negro certainly are not so favorable as in the white. It is a well-known fact that the large majority of the colored race are totally indifferent to the circumstance that they have syphilis when no lesions are manifest, that as long as they can see outward evidences they will take treatment, but when these evidences disappear they become remiss, and either stop treatment altogether or take it so sporadically as to be of little or no benefit.

On the other hand, as we have observed, the negro certainly is less prone to develop the central nervous system sequellæ, especially paresis and tabes, than the white, although arteritis, aortitis, etc., are quite common and quite frequently result in death.

PROPHYLAXIS

In discussing the prophylaxis of syphilis, whether in the white or black, it must be considered from the standpoint of personal measures and public measures.

Hazen[10] believes that it is questionable whether adult negroes should be taught the use of prophylactic packages. With this view we can not agree. Certainly at least a small percentage of negroes taught the use of such measures would employ them, but the prevention of even a few cases of syphilis is worth while.

In the Army naturally the negro is under the same regulations as the white in regard to the use of prophylaxis after sexual indulgence. Briefly these regulations require that if a soldier develops venereal disease and has failed to report for the prescribed prophylaxis he shall be tried by court martial. Our records show that there have been practically the same number of whites tried for this offence as negroes.

Certain of the public measures of prophylaxis, as Hazen has pointed out, are of little or no avail in the negro. For example, it is difficult to persuade the average negro of the poorer type that sexual indulgence is wrong, even if he is in the actively infectious stage of syphilis. Therefore lectures, exhibits, moving pictures, etc., on sex hygiene subjects are of less value to the negro than to the better educated white. However, Hazen has shown that if the housing problem of the negro might be improved there might be a decrease in syphilis.

Syphilis should be made a reportable disease in all places as it now is in many, and not only should it be reportable, but a severe penalty should be imposed on physicians for failure to report their cases.

Free clinics should be available where all cases of syphilis could receive modern treatment and all cases should be compelled to take such treatment until cured.

Of course these latter remarks apply to the white as well as to the black.

TREATMENT

The treatment of syphilis in the negro is the same as the treatment of this disease in other races, and as far as we have been able to observe the response to treatment is the same.

It has been alleged that the negro more frequently shows a severe reaction to the administration of arsphenamine than the white. This we have been unable to observe. In fact, in several hundreds of injections in the present series of cases we have seen but two or three reactions and none which might be termed severe. Furthermore, we have learned that many times colored soldiers who had received injections of arsphenamine have been put on guard duty soon afterward, contrary to our directions, without any ill effects.

Owing to the poor buccal hygiene of the average negro it might be expected that this race would tolerate less mercury without stomatitis than the white. However, although the average negro does have poor mouth hygiene he usually has very good teeth, and we have found his tolerance for mercury fully the equal of the white.

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PNEUMONIAS FOLLOWING INJECTIONS OF ARSENOBENZOL*

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THE ordinary reactions following intravenous injections of the various arsenic preparations in the treatment of syphilis and other conditions are well known. A number of severe and unusual reactions occurred at this hospital which are of sufficient interest and importance to warrant publication.

Intravenous injections of arsenobenzol were given to nine syphilitic soldiers on November 23, 1918. All had symptoms immediately after the injection, or within a few minutes, of irritation to the respiratory organs, and within a few days developed bronchopneumonias. They were critically ill, but made complete recoveries.

This article will describe the clinical features of the reactions, the preparation of the solution, the technic of its injection, and then attempt to determine the cause of the reactions.

REACTIONS IMMEDIATELY FOLLOWING THE INJECTIONS

Untoward symptoms began during, immediately afterward, or within a few minutes following the injections in all of the patients and compelled them to go to bed. These symptoms were pain in the chest, cough, dyspnea, and prostration.

Pain varied from a sense of pressure to a sharp cutting pain in the anterior and lateral part of the chest which made it impossible to take a deep inspiration.

Some also complained of pain in the course of the injected vein and some of a burning in the throat. *Cough* was short and catching, mostly unproductive, but a few had frothy or blood-stained mucous expectoration. *Dyspnea* was extreme. The sitting position had to be assumed in most of the cases. The *pulse* was moderately increased in frequency and was soft; *febrile reaction* was mild. *Physical examinations* of the chests were negative. In short, there were immediate evidences of irritation of the respiratory organs with accompanying febrile reaction and prostration. Seven had nausea or vomiting. None had diarrhea.

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*Authority to publish granted by the Surgeon-General's Office, Washington, D. C.

THE BRONCHOPNEUMONIAS

Clinical.—After from one to three days physical signs and clinical symptoms of bronchopneumonias developed in eight of the nine cases. In the remaining case the lungs showed no abnormal signs, but the symptoms and general clinical course were exactly the same as in the other eight and it is believed that he also had a bronchopneumonia.

The outstanding feature was the *dyspnea,* the respiration reaching 64 in one of the cases. All of them at some time during the course of their illness had as high as 46 respirations per minute. The number of respirations was out of proportion to the physical signs, the pulse rates, and the temperatures.

Cough was short and distressing. *Expectoration* was bloody in four cases, the sputum containing more blood than an ordinary pneumonia. None had hemoptysis. *Pulses* ranged from 88 to 116 and were soft. The highest temperature was 103.4° by mouth. *Cyanosis* was slight in three, in the others it was absent. The *physical signs* were like those found in bronchopneumonia from other causes. Slight dullness at one or both bases with diminished breathing or subcrepitant or crepitant rales; or bronchial breathing; or the same findings without percussion changes; or small scattered areas of bronchial breathing with increased whispering voice. In no cases were the signs widespread.

The chests on the whole were dry having only a few moist rales, except at the places where the definite physical signs of bronchopneumonia existed, and even here the moist rales were relatively few in numbers.

Eye Back Grounds.—One case showed a mild optic neuritis in the left eye which it is believed was caused by arsenic. He had absolutely no subjective eye symptoms and made a perfect recovery.

The general course of the pneumonias was that of a moderately severe type, with extreme dyspnea and distressing pain in the chest. There were no mental symptoms nor skin rashes.

Laboratory.—Urine in seven cases, showed albumin; two of these seven cases had granular casts. These findings all disappeared. In no case was blood found and at no time did any uremic symptoms appear. *Leucocyte counts* were made two or three times on each patient during the febrile stage. The highest count was 30,800, the lowest 8,400. With but few exceptions the leucocytes ranged from 16,000 to 22,000. The polynuclear increase was moderate.

Blood Cultures.—Showed Streptococcus hemolyticus, 3 cases; unidentified diplococci, 2 cases; sterile, 4 cases. In the *sputum,* 6 had Staphylococcus aureus; 2 Streptococcus hemolyticus; and one had an unidentified diplococcus.

SUMMARY

1. Nine cases of syphilis were injected with exactly the same solution and technic, each having an immediate reaction which was followed by a bronchopneumonia.

2. All cases were critically ill, extreme dyspnea being the outstanding feature.

3. The recovery was complete in each case.

The Sterilization, the Arsenobenzol Solution, and the Technic of Its Injection

1. The *water* used for dissolving the arsenobenzol was distilled, was from 5 to 7 days old, and contained a few Gram-positive diplococci.

2. The *15 per cent sodium hydroxide* solution used for neutralizing the arsenobenzol solution was fresh and sterile.

3. The *arsenobenzol ampules* seemed intact and nothing unusual was noted in the appearance of the drug.

4. *Experiments to determine the efficiency of sterilization* as carried out in connection with the arsenobenzol injections on November 23, were made with exactly the same apparatus and technic. It was found that sufficient heat had been employed to kill any nonsporulating organisms and cultures made from the water containing the Gram-positive diplococci, after this heating, were sterile.

5. The *solution of arsenobenzol* was made by dissolving the contents of seven tubes, (each containing 0.6) in 175 c.c. of water in a sterilized bottle containing sterilized glass beads and skaking until the

drug had been entirely dissolved. Seven pipettes of sodium hydroxide solution were added, precipitation of the drug taking place as usual. The alkali was then added drop by drop, a few drops only being necessary to produce a clear solution. The solution was filtered through a sterile gauze sponge into a graduate which held the entire quantity.

6. The injection was immediately made by the syringe method, each patient receiving 18 to 20 c.c. of the solution which contained 0.467 of the drug. The syringe and needles were boiled two to three minutes between each injection and the entire time consumed in injecting the nine cases was between 35 and 40 minutes.

Conclusion as to the Cause of the Reactions

1. *The reactions were not caused by an undissolved substance.* Undissolved arsenobenzol, glass splinters, or other foreign bodies would have gravitated to the bottom of the graduate. An undissolved substance could have caused one or several reactions but not nine reactions.

2. The *reactions were not caused by living bacteria* because:

(a) The irritating effect was immediate.

(b) Bacteria in numbers large enough to produce an immediate reaction of such severity would have passed through the lungs into the general circulation and caused additional infections in other parts of the body, at least in some of the cases.

(c) Laboratory tests conducted under exactly the same conditions as existed at the time the injections were given, showed that the organisms present in the water were killed and the temperature was sufficient to destroy any ordinary nonsporulating organisms.

3. The *water was not responsible because*:

(a) Water from the same source and equally old had been used a number of weeks without unusual reactions.

(b) Water which is not freshly distilled frequently gives reactions because of the toxic substance which it contains. Ravaut has, however, shown that these could be avoided by using small quantities of water and thus injecting a smaller quantity of toxic substance. Water was injected in these cases to the amount of but 18 to 20 c.c. All kinds of water have been used for arsenic injections without causing the immediate, irritating, and *unusual* effects of the injections in these cases.

4. The *alkali was sterile.*

5. The *patients themselves were not specially susceptible* to this drug. All had previously been injected with the same or similar remedies from six to twenty-five times with only an occasional gastro-intestinal irritation.

6. The *technic was not at fault.* The operator, a captain of the medical corps, was experienced, had used exactly the same technic with the same drug and the same concentration in about 200 cases without unusual reactions. The amount of sodium hydroxide was the same as had been used with former injections and it precipitated and dissolved the arsenobenzol as usual.

7. The *reactions* were immediate and were caused by chemical irritation.

8. The only factor in the solution remaining to be considered is the arsenobenzol. By exclusion it *would seem that the drug was responsible for the reactions.* Six tubes of this drug, Lot 907, all that remained of the last supply purchased were forwarded to the Surgeon General for examination. Although the lot number of the tubes which were used is unknown, it is assumed that they belonged to this same lot.

COMMENTS FROM THE OFFICE OF THE SURGEON GENERAL ON THESE REACTIONS

1. "The only explanation other than the one given which occurs to me is that the method of giving a concentrated solution may have something to do with the results. However, the fact that the same technic was used in 200 cases without unusual reactions must be considered.

2. "From our previous experience it is very possible that this salvarsan will pass all the tests required, and still be able to produce toxic effects especially in a concentrated solution."—W. J. Nichols, Lt. Col. M. C.

1. "This arsenobenzol Lot No. 907 was tested a year ago and passed at 90 mg. per kilo. This week (January 25, 1919) it has been tested again and passed at 100 mg. per kilo. Apparently, some factor other

than the essential toxicity of the preparation must have caused these bad results.''—G. W. McCoy, Director Public Health Service.

Colonel F. F. Russel calls attention to page 30, *Manual of Treatment of the Venereal Diseases,* second edition, in which directions are given about the water to be used and also in regard to the dilution which read as follows:

''It is important that freshly distilled water be used for arsphenamine solution. Thirty c.c. of water per decigram of arsphenamine is a safe dilution.''

COMMENT ON ARTICLE OF MAJORS SCHWERDTFEGER AND TINKER ON "PNEUMONIAS FOLLOWING INJECTIONS OF ARSENOBENZOL"

By JAY FRANK SCHAMBERG, M.D., Philadelphia, Pa.

(Received for publication, May 26, 1919)

THE writers of the above article report a series of intravenous administrations of arsenobenzol to nine soldiers on Nov. 23, 1918, immediately followed by evidences of respiratory irritation, and within a few days by bronchopneumonia. In a search for the cause, the authors critically analyze the question of water sterilization, the method of preparation of the solution and the technic of injection, and, after eliminating each of these as a possible factor, come to the conclusion that *"it would seem that the drug was responsible for the reactions."*

With commendable fairness the authors append to their report, the statement of Dr. G. W. McCoy, Director of the U. S. Public Health Laboratories, as to the toxicity tests carried out on the product in question, and a statement from Col. F. F. Russel in which he calls attention to page 30 of the *Manual of Treatment of Venereal Diseases* in which directions as to the concentration of solutions of arsphenamine are given as follows: "It is important that freshly distilled water be used for arsphenamine solution. Thirty c.c. of water per decigram of arsphenamine is a safe dilution."

The explanation of the cause of the reactions reported in the communication, is succinctly and correctly answered by Col. Russel, when he calls attention to the simple statement in the "Manual" that "thirty c.c. per decigram of arsphenamine is a safe dilution."

In the cases of pneumonic complications referred to, 0.467 grams of arsphenamine were given in 18 to 20 c.c. of water or 1 decigram in about 4 c.c. of water. The contrast between the instructions in the "Manual," and the technic employed in this connection, is striking.

But is there actual evidence to indicate that the high concentration of the solution was the real cause of the bronchopneumonias?

MacKee in 1912, observed that intravenous injections of arsphenamine in acid solution produced a precipitate in the blood and a reaction in the patients proportionate to the concentration of the solution and rate of injection. Joseph demonstrated that acid solutions of arsphenamine produce a precipitate in the blood which may actually be seen in the lungs and in the right ventricle of experimental animals. He assumed that emboli might develop in the capillaries of the lungs. Von Miessner found on autopsy thromboses in the lungs of cattle suffering from hoof and mouth disease that had received acid solutions of salvarsan. Joseph later published experiments on the influence of acid solutions of salvarsan on the blood in the test tube. One-tenth of one per cent solutions had no effect on the consistence of the blood, but in a concentration of one per cent or more, the precipitate may be so pronounced as to cause the blood to lose its fluid nature.

Danysz and other French writers have called attention to the observation that arsphenamine neutralized with sodium hydrate according to the instructions of Ehrlich (i. e., just sufficient to clear up the precipitate) produces the mono-sodium salt of arsphenamine, and that this salt is capable of producing a precipitation in the blood, whereas additional alkali will produce the disodium salt which does not precipitate. These observations have been confirmed in our laboratories.

There can be no doubt that the use of a strongly concentrated solution of arsphenamine, particularly if the addition of the alkali has been extremely accurate (according to present methods of neutralization), is much more prone to produce a precipitate in the blood. This precipitate may be carried to the capillaries of the lungs and cause substernal pain, dyspnea, cyanosis, cough and a subsequent bronchopneumonia.

I have knowledge of three patients injected with an acid solution of arsphenamine by a physician who thought that the sole purpose of the alkali was to clear the solution; having obtained a clear solution without the addition of the alkali, he thought this was superfluous. Fortunately no bad symptoms followed, by reason of the fact that the physician had used a very dilute solution, 6 decigrams in 300 c.c. of water. Had he used 20 c.c., he would have killed his patients, as happened on one or more occasions in the early days of the use of salvarsan.

I know of an instance of a sudden death and several severe reactions characterized by substernal pain, followed by fever, subcrepitant rales, and prostration, where the physician administered 0.6 arsphenamine in 50 c.c. of water to a group of women, and owing to doubt as to overneutralization, added several drops of a 10 per cent solution of hydrochloric acid. Here the acidity and the concentration caused the fatal result.

The one feature in the report of Majors Schwerdtfeger and Tinker that possibly needs clarification, is the statement that the "same concentration was used in about 200 cases by the Captain in charge, without unusual reactions." Without definite data as to the comparative amounts of alkali added to the other lots and to the one in question, it would be difficult to express an opinion. It is possible that less alkali was added to the ampules which caused the reactions. The question of the *rate of injection* is likewise an important consideration. Where a concentrated solution is administered with a piston syringe, there is no constancy of the rate of the flow as occurs with a gravity burette, and in the hurry of multiple injections, the rapidity of infusion of the solution may be unconsciously increased.

Finally, the fault lay with the operator, for the instructions accompanying the ampules state distinctly a concentration of 0.6 grams in 100 to 120 c.c. of water, instead of which nearly 0.5 grams were given in less than one fifth of this volume.

NOTE.—Since the above was written, Dr. G. W. McCoy, Director of the Hygienic Laboratory at Washington, has forwarded a communication to the various laboratories making arsphenamine, suggesting that a special notice be sent out with the drug, reading as follows: "This drug shall be administered in a dilution not more concentrated than 0.1 gram in 30 c.c. of fluid, and the time of administration should be at least two minutes for each 0.1 gram."

STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. IV

A GENERAL STUDY OF THE COMPLEMENTS OF VARIOUS ANIMALS WITH SPECIAL REFERENCE TO HUMAN AND GUINEA PIG COMPLEMENTS AND METHODS OF COLLECTION

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FOLLOWING the custom of Bordet who employed guinea pig serum for complement in his original complement-fixation experiments, Wassermann adopted the serum of this animal for complement in his syphilis reaction, and this practice continues in the majority of laboratories. Whether or not Bordet and Wassermann decided upon this animal because of its general laboratory usefulness and availability or after comparative experiments with the sera of other animals we are unable to state, but such experiments by others have indicated that the serum of the guinea pig is best suited for complement among the sera of the lower animals and that Bordet's choice was both excellent and fortunate. The only other complement serum entering seriously into competition with that of the guinea pig is human serum and a decision on which of these is better adapted for a standardized complement-fixation technic has been reached only after a great deal of experimentation and comparative tests employing both sera.

That the complement employed in the Wassermann and other complement-fixation tests may vary sufficiently in essential properties to constitute an important source of error and a cause for variation in results with the same serum in different laboratories is generally accepted, and a thorough practical knowledge of the properties insofar as they concern the phenomenon of complement fixation, is required for the conduct of the Wassermann test under acceptable conditions.

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*Investigation aided by funds accruing from the dispensing of arsphenamine.

REQUIREMENTS OF AN ACCEPTABLE COMPLEMENT SERUM

Because of our lack of definite information regarding the mechanism of complement fixation we must accept the total of practical experience of investigators in this field of immunity as our guide and upon this basis it may be stated that an acceptable complement serum should possess certain properties as follows:

1. *A high degree of hemolytic activity for the erythrocytes of the indicator antigen,* that is, prove hemolytic in relatively small doses; even if satisfactory in other respects a complement required in large amounts for complete hemolysis is apt to prove unsatisfactory if we accept the statements of Noguchi and Bronfenbrenner[1] that fixation is not selectively directed towards complement, but that an excess of indifferent serum proteins may result in their fixation by syphilis antibody and antigen and thereby deviate complement from fixation by syphilis antigen and antibody resulting in erroneous reactions tending toward falsely negative results.

2. *A high degree of fixability by the antigen-antibody complex;* upon this property largely depends the delicacy of the reaction and serologists are too prone to overlook the fact that the complements of all animals vary considerably in their fixability. We have never found a complement serum of persons or guinea pigs totally devoid of fixability when tested with several different syphilitic sera although they may not be fixed by every syphilitic serum. In other words *a complement may be fixed by one serum and antigen and not by another,* and it is an error to conduct Wassermann reactions with the complement serum of one animal and a fruitful cause for varying results when several serologists test the same serum, and particularly if this serum yields a weakly positive reaction.

3. *The complement serum must not be too susceptible to non-specific fixation,* that is, too sensitive to the so-called anticomplementary effect of serum alone and antigen alone; this is a factor of much importance discussed later in this paper and one generally overlooked in reference to complement.

4. *The complement serum should be adaptable to the hemolytic system being employed,* that is, be free, or largely so, of agglutinins for the corpuscles of the indicator antigen and also of hemolysin for these cells; the agglutinin is of more importance, and when present,

as is likely to be the case in human serum, frequently interferes with hemolysis and particularly in an antihuman hemolytic system.

5. *Availability* which refers to the readiness, ease and economy with which this constituent of the Wassermann test may be supplied.

SCOPE OF INVESTIGATION

With these criteria in mind we have devoted a large amount of time to studies with complement sera from a variety of animals with particular attention to guinea pig and human serum complements inasmuch as these are the only ones generally employed; in this communication are recorded the results of the following investigations:

1. A study of serum complements for natural agglutinins and hemolysins insofar as these concern the adaptability of these complements for the Wassermann reaction.
2. Comparative studies of the hemolytic activity and fixability of various complements, and particularly those of persons and guinea pigs.
3. A study of the variation in hemolytic activity and fixability of various complements and particularly those of persons and guinea pigs.
4. A comparative study of the influence upon the Wassermann test conducted with a single complement serum and a mixture of several complements.
5. The influence of the method of collection and preparation of complement serum upon its properties.
6. With guinea pig complement the influence of age, sex, general health, diet, repeated bleedings and anesthesia of the animal upon the properties of the complement.
7. A method for the collection of complement serum.

Inasmuch as human complement is being used more frequently as in the Thompson, Noguchi homohemolytic, Bronfenbrenner and Schlesinger, Myer, Hecht-Gradwohl, Bartlett and O'Shansky and other tests, we have given the subject particular attention, our results being published separately;[2] since the preservation of complement may be necessary and advisable from the standpoint of economy and convenience, the present study has been extended to include this phase,[3] and likewise special attention has been given the subject of methods for complement titration.[4]

Part 1

THE PRESENCE OF NATURAL HEMAGGLUTININS AND HEMOLYSINS IN THE COMPLEMENTS OF PERSONS AND VARIOUS LOWER ANIMALS

While the erythrocytes of the chicken, ox, horse, guinea pig and other animals have been advocated by certain serologists as indicator antigen for the Wassermann test largely on the basis of the presence or absence of natural hemolysins in human serum for these cells and the influence they may have on the results of the Wassermann test, less attention has been given the presence of natural hemolysins and hemagglutinins in the complement serum and the possible influence they may exert upon the results of the test. We have studied the complements of persons, guinea pigs, rats, rabbits, sheep, hogs and oxen from this angle for natural agglutinins and hemolysins for sheep and human cells; the erythrocytes of other animals have not been employed because the choice of a hemolytic system has been largely narrowed down to the antisheep and antihuman, as will be discussed in a succeeding paper of this series.

From the standpoint of influence upon the Wassermann test the presence of agglutinin in the complement serum for the erythrocytes of the indicator antigen is of more importance than the presence of hemolysin, inasmuch as the former may readily interfere with hemolysis; in the antihuman hemolytic system for example, hemagglutination is frequently very disturbing and is to be attributed not only to the possible presence of agglutinin for human cells in the immune hemolytic serum (amboceptor) but likewise to its presence in the human serum being submitted to the Wassermann test. Natural hemolysin in a complement serum for the particular erythrocytes being employed tends to lower the complement unit for these cells and in this manner may be desirable, and a possible explanation for a part at least of the variation in complement activity of different sera; if the complement serum is titrated the presence of natural hemolysin for the erythrocytes of the indicator antigen is adjusted, but in general terms a complement serum free of hemolysin is more desirable by removing a possible source of error.

Natural Hemagglutinins in the Sera of Various Animals.—In conducting the tests for agglutinin for sheep erythrocytes, twelve complement sera from the various animals studied were heated at 56° C. for thirty minutes and used in dose of 0.1 c.c. with 0.1 c.c. of a 5 per cent suspension of washed cells of *one sheep;* 0.8 c.c. of saline solution was added and incubation conducted in a water-bath for one hour, readings being made the following morning. Duplicate tests were set up with the washed erythrocytes of *one person.* The results are summarized in Table I.

TABLE I

PERCENTAGE OF SERA OF PERSONS AND VARIOUS LOWER ANIMALS SHOWING THE PRESENCE OF AGGLUTININS FOR SHEEP AND HUMAN ERYTHROCYTES

Corpuscles	PERCENTAGE OF SERA SHOWING PRESENCE OF AGGLUTININS						
	Human Sera	Guinea-pig Sera	Rat Sera	Rabbit Sera	Ox Sera	Sheep Sera	Hog Sera
For Sheep Corp.	10%	none	none	none	none	occasional	none
For Human Corp.	22%	none	none	none	16%	none	60%

TABLE II

AGGLUTININS IN INACTIVATED HUMAN SERA FOR THE ERYTHROCYTES OF DIFFERENT SHEEP

SERUM NO.	RESULTS WITH VARIOUS ERYTHROCYTE SUSPENSIONS					
	Sheep 1	Sheep 2	Sheep 3	Sheep 4	Sheep 5	Sheep 6
1	+*	—	—	—	—	—
2	+	+	+	+	+	—
3	—	—	—	—	—	—
4	—	—	—	—	—	—
5	—	—	—	—	—	—
6	—	—	—	—	—	—
7	—	—	—	—	—	—
8	—	—	—	—	—	—
9	+	+	+	+	+	+
10	+	+	—	+	—	—
11	—	—	—	—	—	—
12	—	—	—	—	—	—
13	—	—	—	—	—	—
14	—	—	—	—	—	—
15	+	—	+	+	+	—
16	+	+	—	—	—	—
17	+	+	—	+	—	—
18	+	—	—	—	—	—
19	—	—	—	—	—	—
20	—	—	—	—	—	—
21	—	—	—	—	—	—
22	—	—	—	—	—	—
23	—	—	—	—	—	—
24	+	—	—	+	—	—
25	—	—	—	—	—	—

* + = agglutination; — = no agglutination.

The results shown in Table I are only approximately correct inasmuch as they are based upon tests with the corpuscles of *one person* *and one sheep as stated above; additional experiments*[5] *have shown that different results may be observed when these sera are tested with the corpuscles of several persons and several sheep instead of with the cells of one person and one sheep.* In Table II, for example, are shown the results of agglutinin tests with the sera of twenty-five persons and the corpuscles of six different sheep and in Table III the results of similar tests with the corpuscles of six different persons.

TABLE III

AGGLUTININS IN INACTIVATED HUMAN SERA FOR THE ERYTHROCYTES OF DIFFERENT PERSONS

SERUM NO.	RESULTS WITH VARIOUS ERYTHROCYTE SUSPENSION					
	Person 1	Person 2	Person 3	Person 4	Person 5	Person 6
1	—*	—	—	—	—	—
2	—	—	—	—	—	—
3	—	—	+	+	—	+
4	+	—	—	+	—	—
5	+	—	+	+	+	+
6	+	—	+	+	+	+
7	—	—	—	—	—	—
8	—	—	—	+	+	—
9	—	—	—	+	—	—
10	—	—	—	—	—	—
11	+	—	+	+	+	+
12	+	—	+	+	+	+
13	+	—	+	+	—	—
14	+	—	+	+	+	+
15	—	—	—	—	—	—
16	+	—	+	+	+	+
17	—	—	—	+	+	—
18	+	—	+	+	+	+
19	—	—	—	+	+	—
20	—	—	—	+	—	—
21	+	—	+	+	+	+
22	—	—	—	+	—	—
23	+	—	+	+	+	+
	+		+	+	+	+
	+		+	+	+	+

* + = agglutination; — = no agglutination.

As shown in these tables *from 4 to 36 per cent of human sera may contain agglutinin for sheep cells depending upon the corpuscles employed and from 4 to 80 per cent of human sera may contain agglutinin for human cells depending upon the particular corpuscles employed.* The results of agglutinin tests with 100 human sera employing the corpuscles of one person and a mixture of corpuscles of four persons as antigens, are shown in Table IV; these tests were not conducted at the same time and with the same cells but were done at different times with the single and mixed corpuscle suspensions; the results show the influence of group agglutinins and what may be expected in this direction when erythrocytes are chosen at random for indicator antigen in the antihuman system.

TABLE IV

AGGLUTININS FOR HUMAN RED BLOOD CORPUSCLES IN INACTIVATED HUMAN SERA

Total Sera Tested	Percentage Sera Showing Agglutination with the Erythrocytes of one Person	Percentage Sera Showing Agglutination with a Mixture of Erythrocytes of Four Persons
100	22%	47%

Inasmuch as most interest concerns the presence of hemagglutinins in human and guinea pig complements because these are widely employed for complement in the Wassermann test and its numerous modifications, further studies were made with these complements for the presence of agglutinins for the erythrocytes of various animals and the results are given in Tables V and VI.

TABLE V

PERCENTAGE OF HUMAN SERA IN AMOUNT OF 0.2 C.C. SHOWING THE PRESENCE OF AGGLUTININS FOR THE ERYTHROCYTES OF VARIOUS ANIMALS

FOR HUMAN CORP.	FOR SHEEP CORP.	FOR OX CORP.	FOR CHICKEN CORP.	FOR GUINEA-PIG CORP.
47%	16%	occasional	10%	28%

TABLE VI

PERCENTAGE OF GUINEA PIG SERA IN AMOUNT OF 0.1 AND 0.2 C.C. SHOWING THE PRESENCE OF AGGLUTININS FOR THE ERYTHROCYTES OF VARIOUS ANIMALS

FOR GUINEA PIG CELLS		FOR CHICKEN CELLS		FOR HUMAN CELLS		FOR OX CELLS		FOR SHEEP CELLS	
0.1 c.c.	0.2 c.c.	0.1 c.c.	0.2 c.c.	0.1 c.c.	0.2 c.c.	0.1 c.c.	0.2 c.c.	0.1 c.c.	0.2 c.c.
None	occasional	none	none	occasional	occasional	none	none	none	none

The results summarized in Tables V and VI were based upon tests with a large number of sera and single corpuscle suspensions, but indicate that guinea pig serum seldom contains agglutinin for the corpuscles of persons, sheep, and other animals whereas a relatively large percentage of human sera contains agglutinins for the erythrocytes of various animals and particularly for human cells.

Influence of Agglutinins upon Hemolysis.—All serologists of experience have noted retardation or incomplete hemolysis when agglutination of the red corpuscles has taken place; this is particularly true of the antihuman hemolytic system due to the presence of agglutinins in the rabbit immune serum and the patient's serum being tested. We have also noted on frequent occasions that agglutination with an antihuman hemolytic system was particularly well marked in those tubes containing the ordinary antigens employed in the conduct of the Wassermann test, rendering the readings difficult and open to error.

Guinea pig complement occasionally contains agglutinins for human corpuscles and their influence has frequently been evident in titration of the same complements diluted 1:10 and 1:1½; paradoxical as it appears hemolysis was better marked and more satisfactory with the 1:10 than with the 1:1½ dilution, both dilutions being used in titrations employing the same amount of antihuman rabbit hemolysin (2 units) and 0.1 c.c. of 5 per cent cells (Table VII), these results being ascribed to the lesser amounts of agglutinin in the higher dilution of complement serum.

TABLE VII

THE INFLUENCE OF AGGLUTININS FOR HUMAN CELLS IN GUINEA PIG COMPLEMENT UPON HEMOLYSIS

PIG NO.	DILUTION	DOSES OF COMPLEMENT AND RESULTS									
		.02	.04	.06	.08	.1	.2	.3	.4	.5	.6
1	1:10	N. H.	N. H.	S. H.	M. H.	H	H	H	H	H	H
	1:1½	N. H.	M. H.	H	H	M. H.	N. H.	N. H.	N. H.	N. H	N. H.
2	1:10	N. H.	M. H.	H	H	H	H	H	H	H	H
	1:1½	N. H.	N. H.	N. H.	S. H.	M. H.	M. H.	M. H.	M. H.	M. H.	M. H.
3	1:10	N. H.	S. H.	H	H	H	H	H	H	H	H
	1:1½	N. H.	N. H.	S. H.	S. H.	S. H.	S. H.	M. H.	M. H.	M. H.	H

N. H. = no hemolysis; S. H. = slight hemolysis; M. H. = marked hemolysis; H = hemolysis (complete).

Prevention of Hemagglutination.—Insofar as we can ascertain the only practical means of overcoming the influence of hemagglutinins in the amboceptor serum, complement or patient's serum, is by the use of the most powerful hemolysins available capable of sensitizing cells in amounts or dilutions beyond the presence of agglutinins.

No method has yet been described for removing agglutinins from amboceptor serum without removing in whole or large part the hemolysin.* Since Dreyer and others have found that formalin tends to prevent spontaneous agglutination of typhoid bacilli, we have conducted numerous experiments along this line but without good practical results; formalin in high concentration as from 2 to 5 per cent in physiologic saline solution prevents hemagglutination, but these amounts of formalin are hemolytic within several hours and highly anticomplementary. Likewise varying concentrations of sodium chloride have been employed by reason of their influence toward the prevention of spontaneous agglutination of bacteria and leucocytes, but no concentration has been found that is effectual against large amounts of hemagglutinin; solutions of sodium chloride in distilled water varying from 1.2 to 1.6 per cent tended to inhibit the agglutination of human corpuscles by human serum but exhibit no appreciable influence in the presence of the agglutinin contained in rabbit antihuman serum.

Of course hemagglutinins are readily removed from an active serum by bringing it to a low temperature and adding chilled washed corpuscles, and centrifuging the mixture for the serum after standing for at least one hour; in a series of Wassermann tests with a large number of human sera before and after removal of agglutinin for the human cells of the indicator antigen in an antihuman hemolytic system something was gained in the way of sharper results by absorption and removal of the agglutinin, but not enough to warrant the time and extra labor involved and particularly when a powerful amboceptor serum was available.

Natural Hemolysins in the Complement Sera of Various Animals.—In conducting these tests the fresh active sera of persons and various of the lower animals were used in doses of 0.1 and 0.2 c.c. with 0.1 c.c. of 5 per cent suspensions of washed erythrocytes and 0.8 c.c. saline solution; incubation was conducted in the water-bath for one hour and the readings made the following day. The results show the total hemolytic activity of the sera for the particular erythrocytes employed depending upon the presence of hemolytic complement and natural hemolysin, both thermolabile and thermostabile.

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*Recent experiments in these laboratories by Sands and West have shown that drying rabbit antihuman serum results in the removal of large amounts of hemagglutinin without commensurate removal of hemolysin; similar results were secured by filtering diluted serum through porcelain.

The results of tests conducted with sera of twenty-five different persons, sheep, rats, rabbits, hogs and oxen for the presence of natural antisheep and antihuman hemolysins are shown in Table VIII.

TABLE VIII

PERCENTAGE OF SERA OF PERSONS AND VARIOUS LOWER ANIMALS SHOWING THE PRESENCE OF HEMOLYSINS FOR SHEEP AND HUMAN ERYTHROCYTES

CORPUSCLES	PERCENTAGE OF SERA SHOWING HEMOLYSIS						
	Human	Sheep	Rat	Rabbit	Hog	Guinea Pig	Ox
For sheep corpuscles	95%	occasional	65%	16%	96%	40%	occasional
For human corpuscles	4%	none	40%	65%	40%	5%	98%

TABLE IX

NATURAL HEMOLYSINS IN ACTIVE HUMAN SERA FOR THE ERYTHROCYTES OF DIFFERENT PERSONS

SERUM NO.	RESULTS WITH VARIOUS ERYTHROCYTE SUSPENSIONS					
	Person 1	Person 2	Person 3	Person 4	Person 5	Person 6
1	—[*]	—	—	—	—	—
2	—	—	—	—	—	—
3	—	—	—	—	—	—
4	—	—	+	+	+	—
5	—	—	—	—	—	—
6	—	—	+	+	+	—
7	—	—	—	—	—	—
8	—	—	+	+	+	—
9	—	—	+	—	+	—
10	—	—	—	—	—	—
11	—	—	+	+	—	—
12	—	—	+	+	+	—
13	—	—	—	—	—	—
14	—	—	+	+	—	—
15	—	—	—	—	—	—
16	—	—	—	—	—	—
17	—	—	+	+	+	—
18	—	—	—	—	+	—
19	—	—	—	—	—	—
20	—	+	—	+	+	—
21	—	—	—	—	—	—
22	—	—	+	+	+	—
23	—	—	+	+	—	—
24	—	—	+	+	+	—
25	—	—	—	—	—	—

[*] — = no hemolysis; + = hemolysis.

As shown in Table VIII, human sera contain the highest percentage of hemolysin for sheep cells and ox sera the highest for human cells.

These figures, however, are only approximately correct inasmuch as group hemolysins exist in both human, guinea pig and other sera for human and sheep cells. This fact, of course, is well known in relation to group hemolysins for human cells in human sera and is shown in Table IX where from 4 to 44 per cent of unheated human sera were found to contain hemolysin according to the corpuscles employed. The same condition is true regarding the presence of other hemolysins in human sera, but with antisheep hemolysin the tendency for grouping is not clearly evident, inasmuch as almost 100 per cent of human sera contain antisheep hemolysin (Table X); a similar condition exists in relation to the presence of antihuman hemolysin in unheated ox serum.

TABLE X

NATURAL HEMOLYSIN IN ACTIVE HUMAN SERA FOR THE ERYTHROCYTES OF DIFFERENT SHEEP

SERUM NO.	RESULTS WITH VARIOUS ERYTHROCYTE SUSPENSION					
	Sheep 1	Sheep 2	Sheep 3	Sheep 4	Sheep 5	Sheep 6
1	C*	C	M	C	C	C
2	C	C	C	C	C	C
3	C	C	C	C	M	C
4	C	S	S	N	S	S
5	N	N	N	N	N	N
6	C	C	C	C	C	C
7	M	M	M	C	C	C
8	C	C	C	C	C	C
9	C	C	M	C	C	C
10	C	M	M	C	M	C
11	C	C	C	C	C	C
12	C	C	C	C	C	C
13	C	C	C	C	C	C
14	C	C	M	M	C	C
15	C	C	C	C	C	C
16	C	C	C	C	C	C
17	C	C	C	C	C	C
18	C	C	M	C	C	C
19	C	C	C	C	C	C
20	S	S	N	N	N	N
21	C	C	C	C	C	C
22	C	C	C	C	C	C
23	C	C	C	C	C	C
24	C	C	C	C	C	C
25	C	C	C	C	C	C

*C = Complete hemolysis; M = marked hemolysis; S = slight hemolysis; N = no hemolysis.

Human and guinea pig serum complements being of most interest and importance from the standpoint of the Wassermann reaction, were given particular attention and the results of a large number of tests with both for the presence of various hemolysins are summarized in Tables XI and XII.

TABLE XI

PERCENTAGE OF ACTIVE HUMAN SERA IN AMOUNTS OF 0.1 AND 0.2 C.C. SHOWING THE PRESENCE OF HEMOLYSINS FOR THE ERYTHROCYTES OF VARIOUS ANIMALS

FOR HUMAN CELLS		FOR SHEEP CELLS		FOR OX CELLS		FOR CHICKEN CELLS		FOR GUINEA-PIG CELLS	
0.1 c.c.	0.2 c.c.	0.1 c.c.	0.2 c.c.	0.1 c.c.	0.2 c.c.	0.1 c.c.	0.2 c.c.	0.1 c.c.	0.2 c.c.
6%	9%	95%	100%	78%	90%	93%	100%	98%	98%

TABLE XII

PERCENTAGE OF ACTIVE GUINEA PIG COMPLEMENT SERA IN AMOUNTS OF 0.1 AND 0.2 C.C. SHOWING THE PRESENCE OF HEMOLYSINS FOR THE ERYTHROCYTES OF VARIOUS ANIMALS

FOR HUMAN CELLS		FOR SHEEP CELLS		FOR OX CELLS		FOR CHICKEN CELLS		FOR GUINEA PIG CELLS	
0.1 c.c.	0.2 c.c.	0.1 c.c.	0.2 c.c.	0.1 c.c.	0.2 c.c	0.1 c.c.	0.2 c.c.	0.1 c.c.	0.2 c.c.
5%	40%	40%	70%	32%	50%	40%	55%	occasional	30%

It is worthy of special note that these results are based upon the use of unheated sera and represent the presence of both thermolabile and thermostabile hemolysins; for example, about 100 per cent human sera contain thermolabile antiguinea pig hemolysin, whereas heated sera contain this hemolysin only occasionally. (Table XII).

The results of more detailed studies in this subject are given in a separate communication[5] previously mentioned.

The relation of agglutinins and hemolysins in the same sera for various erythrocytes is very interesting in this connection; guinea pig serum for example contains hemolysins for human, sheep, ox and chicken cells but no agglutinin insofar as these were detectable in a macroscopic technic. Human serum contains many different hemolysins and agglutinins for various corpuscles but there is no strict relationship in the presence of these. Attention has previously been drawn to the difference in hemolytic activity of human serum for the corpuscles of various animals and particularly those of the guinea pig, depending upon whether or not active or heated sera are employed; these results are summarized in Table XIII in which "total hemolytic activity" refers to the presence of complement, thermolabile and thermostabile hemolysins for the erythrocytes of the various animals studied.

TABLE XIII

SUMMARY SHOWING PERCENTAGE OF HUMAN AND GUINEA PIG SERA CONTAINING HEMOLYSINS AND AGGLUTININS FOR THE RED BLOOD CORPUSCLES OF VARIOUS ANIMALS

CORPUSCLES	HUMAN SERUM			GUINEA PIG SERUM	
	Agglutinin	Total Hemolytic activity*	Thermostabile Hemolysin**	Agglutinin	Total Hemolytic activity
Human	4-47%	6%	none	none	5%
Sheep	16%	95%	72%	none	40%
Ox	occasional	78%	47%	none	32%
Chicken	10%	62%	none	none	40%
Guinea pig	28%	98%	5%	none	occasional

*Unheated serum (thermolabile and thermostabile hemolysins).

**Heated serum (thermostabile hemolysins) activated by guinea pig complement (hemolysin-free.)

The general practical results of our studies in this phase of the problem may be summarized as follows:

1. Guinea pig serum being practically free of agglutinin for the erythrocytes of persons, sheep, oxen, chickens, is superior in this respect as complement to human serum which contains these agglutinins in relatively high percentage. In respect to hemolysins in guinea pig complement serum, least is present for homologous cells and next for human cells; for sheep, ox and chicken cells hemolysins are present in about 40 per cent of sera.

2. Human serum contains agglutinins and hemolysins for human, sheep, ox, chicken and guinea pig cells; group agglutinins for human cells are present in a large percentage of human sera according to the cells used in the indicator antigen.

3. *The agglutinins in human sera for the erythrocytes of various animals show grouping* as is well known of the agglutinins for human cells.

4. Insofar as agglutinins are concerned, guinea pig serum complement is equally adapted for any hemolytic system employing human, sheep, ox, chicken or guinea pig cells; human serum is best adapted for an anti-ox hemolytic system and next in order for chicken, sheep, guinea pig, and human hemolytic systems.

5. From the standpoint of the Wassermann reaction, the influence of agglutinins in the complement serum for the cells of the indicator

antigen is minimized by the use of an immune hemolysin of high titer. The presence of agglutinin for human cells in human serum and in the rabbit antihuman hemolytic serum are the most troublesome and constitute a drawback to the antihuman hemolytic system and especially to those modifications of the Wassermann reaction in which human is substituted for guinea pig complement. The majority of serologists have attributed agglutination in the antihuman system to the presence of agglutinin in the rabbit antihuman hemolysin alone and have overlooked the possibility of the presence of this antibody in the human serum being tested for the cells of the particular indicator antigen employed.

Part 2

THE HEMOLYTIC ACTIVITY AND FIXABILITY OF THE COMPLEMENTS OF VARIOUS ANIMALS

A careful review of the available literature and numerous personal inquiries have shown that but two complement sera are in general use, namely, human and guinea pig. The former is employed in a number of modifications of the Wassermann reaction for the main purpose of convenience and economy but guinea pig complement continues to be more widely employed and apparently by reason of precedent and satisfactory personal experience on the part of a large group of serologists. The real criterion of a complement serum should be suitability for a particular hemolytic system and specific *delicacy,* by which we mean that complement is best in the final analysis which yields the most delicate but specific results regardless of the questions of convenience and economy. A decision on this point can only be reached after thorough comparative tests with carefully chosen sera and the same antigen or antigens; the results of our tests comparing human and guinea pig complements from the practical standpoint in actual comparative complement-fixation tests are given in a succeeding paper of this series.[2] In this section we wish to record the results of experiments with a variety of complement sera regarding their hemolytic activity and fixability in the Wassermann system as compared with guinea pig complement.

A surprisingly small amount of investigation has been reported on comparative studies with the complements of different animals; Noguchi and Bronfenbrenner[6] in a thorough study of the complements of the guinea pig, cat, dog, rabbit, rat, hog, ox, sheep and chicken reached the general conclusion that guinea pig complement was best for the rabbit antihuman hemolytic system. These investigators also made the interesting observation that some amboceptors are best reactivated by the complement of the same species, while others may act most strongly when reactivated with the complements of certain suitable heterologous species, and that in general the rabbit was best suited for the production of antihuman hemolysin. Kolmer, Yui and Tyau[7] in a study of the complements of the ordinary white (mus norvegicus var albinus) and wild sewer rats (mus norvegicus) found that they possessed less hemolytic activity for sheep and human cells as compared with guinea pig complement, but that they were quite sensitive to specific fixation in the Wassermann system and could be employed in the serum diagnosis of syphilis, particularly with an antihuman hemolytic system.

(a) *Hemolytic Activity of Various Complements.*—In these experiments the following complements were studied: human, guinea pig, rat, rabbit, sheep and hog with three rabbit hemolysins, namely, antihuman, antisheep and antiox.

TABLE XIV

HEMOLYTIC ACTIVITY OF THE COMPLEMENTS OF THE HUMAN, GUINEA PIG, RAT, RABBIT, SHEEP, HOG AND OX FOR SHEEP CELLS*

ANIMAL	SERIAL NUMBER OF ANIMAL; UNIT OF COMPLEMENT IN AMOUNTS OF UNDILUTED SERUM.											
	1	2	3	4	5	6	7	8	9	10	11	12
Human	0.012	0.015	0.015	0.012	0.01	0.018	0.012	0.02	0.02	0.012	0.015	0.015
Guinea Pig	0.004	0.004	0.005	0.005	0.004	0.004	0.006	0.005	0.004	0.004	0.004	0.004
†Rat	0.015	0.015	0.015	0.018	0.018	0.02	0.02	0.02	0.025	0.015	0.015	0.015
Rabbit	0.015	0.02	0.02	0.025	0.015	0.018	0.018	0.02	0.02	0.025	0.02	0.015
Sheep	More than 0.4	More than 0.4	0.4	More than 0.4	More than 0.4	More than 0.4	0.4	0.38	More than 0.4	More than 0.4	More than 0.4	More than 0.4
Hog	0.015	0.015	0.02	0.02	0.018	0.015	0.02	0.018	0.01	0.015	0.015	0.015
Ox	More than 0.4	More than 0.4	More than 0.4	More than 0.4	More than 0.4	0.4	More than 0.4	More than 0.4	More than 0.4	More than 0.4	More than 0.4	More than 0.4

*Titrated with 0.0005 c.c. rabbit antisheep hemolysin, of which 0.00025 c.c. produced complete hemolysis of 1 c.c. of 2½ per cent suspension of sheep cells with 0.05 c.c. guinea pig complement.

†Mus norvegicus var. albinus.

In determining the hemolytic activity of these complements in the antisheep system, rabbit antisheep hemolysin was employed in dose of two units (see Table XIV) with 1 c.c. of a 2½ per cent suspension of washed sheep cells, varying amounts of complement diluted 1:5 to 1:20 and sufficient saline solution to make the total volume 2 c.c. followed by water-bath incubation for one hour. Similar titrations were conducted with a rabbit antiox system.

TABLE XV

HEMOLYTIC ACTIVITY OF THE COMPLEMENTS OF THE HUMAN, GUINEA PIG, RAT, RABBIT, SHEEP, HOG AND OX FOR HUMAN CELLS*

ANIMAL	SERIAL NUMBER OF ANIMAL; UNIT OF COMPLEMENT IN C.C. UNDILUTED SERUM											
	1	2	3	4	5	6	7	8	9	10	11	12
Human	0.12	0.1	0.1	0.15	0.1	0.12	0.12	0.1	0.08	0.1	0.12	0.1
Guinea Pig	0.04	0.04	0.03	0.03	0.03	0.04	0.04	0.04	0.05	0.04	0.05	0.04
†Rat	0.04	0.06	0.06	0.05	0.08	0.06	0.04	0.06	0.07	0.06	0.08	0.04
Rabbit	0.06	0.06	0.08	0.1	0.1	0.12	0.08	0.06	0.08	0.1	0.1	0.1
Sheep	0.72	0.75	0.75	0.72	0.78	0.75	0.8	0.8	0.8	0.75	0.7	0.72
Hog	0.06	0.06	0.062	0.065	0.065	0.065	0.07	0.07	0.08	0.07	0.062	0.065
Ox	0.05	0.05	0.08	0.08	0.08	0.05	0.08	0.05	0.06	0.08	0.08	0.05

*Titrated with 0.005 c.c. of rabbit antihuman hemolysin of which 0.0025 c.c. produced complete hemolysis of 0.1 c.c. of 5 per cent suspension of human cells with 0.01 c.c. guinea pig complement.

†*Mus norvegicus* var. *albinus*.

In the titration of the various complements in a hemolytic system, two units of rabbit antihuman hemolysin were employed (see Table XV) with 0.1 c.c. of a 5 per cent suspension of washed human cells, varying amounts of diluted complement and sufficient saline solution to make a total volume of 1 c.c. followed by water-bath incubation for one hour.

The results of titrations of twelve different complement sera from the various animals studied are shown in Tables XIV and XV; the results with the antiox system were so similar to those observed with the antisheep that a separate table and description are unnecessary.

As will be noted in these tables the complement sera of these animals varied greatly in their hemolytic activity for sheep and human cells and the individual sera of the same species showed variations to which further reference is made in Part 3 of this paper.

Accepting guinea pig complement as a standard for a comparison, the hemolytic activity of the complements of other animals for sheep and human cells may be expressed as averages in Table XVI. It is to be understood that these figures are not absolute but variable according to the amounts of hemolysin and corpuscles employed in the titration; but since these factors were held rigidly constant in these titrations, the averages may be accepted as expressing the relative hemolytic activities of the respective complements.

TABLE XVI

HEMOLYTIC ACTIVITY OF THE COMPLEMENTS OF VARIOUS ANIMALS FOR SHEEP AND HUMAN ERYTHROCYTES WITHOUT REMOVAL OF THE NATURAL HEMOLYSINS AND AGGLUTININS*

COMPLEMENTS	AVERAGE COMPLEMENT UNITS	
	With antisheep system	With antihuman system
Human	0.015 c.c.	0.12 c.c.
Guinea pig	0.004 c.c.	0.04 c.c.
Rat	0.017 c.c.	0.06 c.c.
Rabbit	0.02 c.c.	0.09 c.c.
Sheep	more than 0.4 c.c.	0.75 c.c.
Hog	0.016 c.c.	0.07 c.c.
Ox	more than 0.4 c.c.	0.07 c.c.

*Each complement is a mixture of six sera of the respective animals.

TABLE XVII

HEMOLYTIC ACTIVITY OF THE COMPLEMENTS OF VARIOUS ANIMALS FOR SHEEP AND HUMAN ERYTHROCYTES BEFORE AND AFTER REMOVAL OF THE NATURAL HEMOLYSINS AND AGGLUTININS*

COMPLEMENTS*	AVERAGE COMPLEMENT UNITS			
	Antisheep system		Antihuman system	
	Before	After	Before	After
Human	0.04 c.c.	0.08 c.c.	0.2 c.c.	0.25 c.c.
Guinea pig	0.006 c.c.	0.008 c.c.	0.04 c.c.	0.04 c.c.
Rat	0.02 c.c.	0.028 c.c.	0.04 c.c.	0.06 c.c.
Rabbit	0.06 c.c.	0.07 c.c.	0.08 c.c.	0.1 c.c.
Sheep	more than 0.4 c.c.	more than 0.4 c.c.	0.12 c.c.	0.12 c.c.
Hog	0.02 c.c.	0.042 c.c.	0.04 c.c.	0.06 c.c.
Ox	more than 0.4 c.c.	more than 0.4 c.c.	0.04 c.c.	0.08 c.c.

*Each complement is a mixture of six sera of the respective animals.

While the results of these titrations as expressed in Table XVI give the relative values of various complements for sheep and human cells, account is not taken of the possible influence of natural hemolysins and agglutinins in the complement sera for sheep and human cells. Human complement for example, is known to contain relatively large amounts of antisheep hemolysin, and ox complement, large amounts of antihuman hemolysin; when these hemolysins are removed by chilling the complements and absorbing the hemolysins with chilled cells at a low temperature, the hemolytic activity of these sera for sheep and human cells respectively is reduced at least one-half, that is, the unit is doubled. The results of a second series of experiments of this kind are summarized in Table XVII, showing the units of complement sera of various animals for sheep and human cells before and after the removal of natural agglutinins and hemolysins; very probably the presence or absence of these natural hemolysins explains in part the differences in hemolytic activity of the complements of animals of different species and also individual variations among animals of the same species. This factor, however, does not explain the whole as, for example, why sheep complement is so poor in hemolytic activity for both sheep and human cells with hemolysins produced in rabbits, or why practically all complements are more hemolytic for human than for sheep cells.

TABLE XVIII

THE AVERAGE HEMOLYTIC ACTIVITY OF THE COMPLEMENTS OF VARIOUS ANIMALS BEFORE AND AFTER THE REMOVAL OF NATURAL HEMOLYSINS AND AGGLUTININS COMPARED WITH THE AVERAGE COMPLEMENT OF THE GUINEA PIG

COMPLEMENT	RELATIVE HEMOLYTIC ACTIVITY*		ABSOLUTE HEMOLYTIC ACTIVITY**	
	Antisheep system	Antihuman system	Antisheep system	Antihuman system
Human	6-7 x weaker	5 x weaker	10 x weaker	6-7 x weaker
Rat	3 x "	about equal	3-4 x "	½ x "
Rabbit	10 x "	2 x weaker	10 x "	2-3 x "
Hog	3-4 x "	about equal	5-6 x "	½ x "
Sheep	70 x "	3 x weaker	70 x "	3 x "
Ox	70 x "	about equal	70 x "	2 x "

*Before removal of natural hemolysins and agglutinins for sheep and human cells.
**After removal of natural hemolysins and agglutinins for sheep and human cells.

As shown in Table XVIII, guinea pig complement is the most active of all included in this study and particularly in an antisheep hemolytic system; in an antihuman system this superiority is still in evidence, but in a lesser degree. Gurd[8] has stated that human complement is more constant and active than guinea pig complement in an antihuman system; our results do not substantiate this claim, but rather corroborate the findings of Noguchi[9] that human complement is only about one-seventh as active as guinea pig complement. This is shown in Tables XVI, XVII, and XVIII, and also in additional studies with twelve different human and pig complements summarized in Table XIX, and showing that the average of guinea pig complement is 6.3 times more lytic for sheep cells than the average of human complement.

TABLE XIX

COMPARATIVE HEMOLYTIC ACTIVITY OF GUINEA PIG AND HUMAN COMPLEMENT SERA FOR SHEEP CELLS

COMPLEMENT	AMOUNT OF TWELVE DIFFERENT SERA (1:20) GIVING HEMOLYSIS (UNIT); C.C.												AVERAGE UNIT
	1	2	3	4	5	6	7	8	9	10	11	12	
Guinea Pig	0.3	0.3	0.3	0.5	0.4	0.3	0.2	0.3	0.3	0.6	0.3	0.5	0.35
Human	2.0	2.0	2.5	2.5	2.0	3.0	2.0	2.0	2.5	2.0	2.0	2.0	2.2

(b) *The Fixability of Various Complements by Syphilis Antibody and Antigen.*—Of greater importance from the standpoint of the Wassermann reaction is a knowledge of the fixability of the complement serum inasmuch as lytic activity alone is no criterion of a suitable complement; it is well known that the complements of different animals vary in susceptibility to fixation by syphilis antibody and antigen and a notable example of the absence of this property has been described by Noguchi in reference to goat serum.

We have conducted a large number of experiments with human, guinea pig, rat, rabbit, sheep, hog and ox complements and particularly with the first two, from the standpoint of susceptibility to fixation by syphilitic serum and antigen by a method similar to that of Browning and McKenzie. Each complement was titrated for hemolytic activity, and the smallest amount giving complete hemolysis designated as a unit. Inactivated syphilitic serum was used in a series of test tubes in constant dose of 0.1 c.c. with five antigenic units of an antigen of aceton-insoluble lipoids; complement was furnished in increasing amounts from one to six units. Antigen, serum and hemolytic controls were included with one to four units of complement, the ensemble being shown in Table XX. With this method we were able to judge more accurately of the fixability of these sera than by the usual technic employing two units. By computing the amount of complement fixed by antigen alone and serum alone and subtracting from the amount fixed by serum and antigen in the fixation series, we were able to express results according to the number of units of complement fixed specifically.

Table XX

Specific and Nonspecific Fixability of the Complements of Various Animals by a Syphilitic Serum and Antigen*

COMPLEMENTS†	COMPLEMENT FIXATION SERIES						ANTIGEN CONTROL SERIES				SERUM CONTROL SERIES				UNITS OF COMPLEMENT FIXED
	1	2	3	4	5	6	1	2	3	4	1	2	3	4	
Human	++++	++++	+++	++	+	..	++++	+	—	—	++++	—	—	—	3
Guinea Pig	++++	++++	++	+	—	—	+	—	—	—	+	—	—	—	2
Rat	++++	++++	+++	++	—	—	+++	—	—	—	+++	—	—	—	2
Rabbit	++++	++++	+	+	—	—	++	—	—	—	+++	+	—	—	1
Sheep	++++	++++	++	+	±	—	+++	++	+	—	+++	+	—	—	0
Hog	++++	++	±	—	—	—	++	—	—	—	++	—	—	—	1
Ox	+++	+	—	—	—	—	+	—	—	—	±	—	—	—	0

*Acetone-insoluble lipoids.

†All complements were mixtures of six different sera of each species of animal. Antihuman hemolytic system.

Considerable variation occurred with the individual sera of each species of animal but the results shown in Table XX of an experiment employing a mixture of six sera of each species in order to give an average for the complement of each animal, expresses our results in a fairly satisfactory manner. In summarizing the results of our experiments it may be stated:

1. Mixtures of several human complements were generally found most susceptible to fixation by syphilis serum and antigen.

2. Guinea pig complement was a close second; rat and rabbit complements usually gave good fixation, and particularly rat complement.

Table XXI

The Fixability of Hog Serum Complement

ANIMAL	DOSES OF COMPLEMENT 1:10						SERUM CONTROLS		ANTIGEN CONTROLS		UNITS OF COMPLEMENT FIXED
	1 unit	2 units	3 units	4 units	5 units	6 units	1 unit	2 units	1 unit	2 units	
Hog No. 1	++	+	—	—	—	—	+	—	+	—	1-2
Hog No. 2	++	++	+	—	—	—	+	—	±	—	2
Hog No. 3	++	++	—	—	—	—	+	—	+	—	1-2
Guinea Pig*	++	++	++	+	+	—	+	—	±	—	4

*Mixed sera of three guinea pigs. Antisheep hemolytic system; antigen of aceton-insoluble lipoids.

3. Of the complements of the larger animals (sheep, hog and ox) only that of the hog was found worth while, but distinctly inferior to the complement of the guinea pig (Table XXI). With these complements the unit is apt to be relatively large, thereby introducing a large amount of serum with the consequence that the serum proteins may interfere with the phenomenon of complement fixation by reason of fixing antigen of complement as described by Noguchi and Bronfenbrenner,[1] resulting in weakly positive or falsely negative reactions.

The Susceptibility of Various Complements to Nonspecific Fixation.—Of considerable interest and importance in this connection is a consideration of the susceptibility of the complements of these various animals to nonspecific fixation by antigen alone and patient's serum alone—well known as the anticomplementary action of antigen and serum. For example, sheep and ox complements usually yield strongly positive reactions, but both are very susceptible to antigen alone and serum alone as shown in Table XX and but slightly to specific fixation in mixtures of antigen and serum. As will be described later, all complement sera become more sensitive to nonspecific fixation and anticomplementary influences according to the method of preparation and age of the serum, but experiments with the complements of all animals included in this study collected in a uniform manner have shown that *guinea pig complement is less susceptible to nonspecific fixation and anticomplementary influences than the complement of any other animal; human complement is more susceptible* and for this reason is more likely to yield unsatisfactory serum and antigen controls in that interference with hemolysis is of frequent occurrence.

Part 3

VARIATION IN THE HEMOLYTIC ACTIVITY AND FIXABILITY OF COMPLEMENT WITH SPECIAL REFERENCE TO HUMAN AND GUINEA PIG COMPLEMENTS

Not only may the complement sera of animals of different species show this marked variation in lytic activity and fixability, but what is of more importance, the complements of animals of the same species may show differences in lytic activity and particularly in fixability by syphilis serum and antigen as shown by Browning and McKenzie[11] and confirmed by the investigations of Clark,[12] Noguchi and Bronfenbrenner,[13] Ottenberg,[14] Detweiler,[15] Ruediger,[16] and others; these investigators have found quite uniformly that guinea pig complement serum is apt to vary more in fixability than in lytic activity and that in order to overcome this source of error a mixture of sera from several pigs should be used.

These warnings have not received the attention they deserve and it is absolutely necessary to control the factor of fixability of complement for acceptable work with the Wassermann and other complement fixation tests. It is a widespread custom and particularly in smaller laboratories, to depend upon the complement serum of one animal; while we have never found a guinea pig complement devoid of fixability when tested with the sera of several syphilitic persons, yet *a complement may not be fixed by one or more particular sera in a series of tests, that is, a complement may be fixed by one syphilitic serum and not by another* and thereby prove misleading. We have found the same to be true of human complement and this fact constitutes one source of error in methods employing the complement of each person's own serum as those of Hecht, Tschernogubow, Thompson, Noguchi, and others to which special attention has been given and the results described elsewhere.[2]

TABLE XXII

VARIATION IN THE HEMOLYTIC ACTIVITY OF HUMAN COMPLEMENT IN AN ANTIHUMAN AND ANTISHEEP HEMOLYTIC SYSTEM

HEMOLYTIC SYSTEM	UNIT OF COMPLEMENT IN C.C. OF UNDILUTED SERA OF 20 PERSONS									
	1	2	3	4	5	6	7	8	9	10
Antihuman........	0.2	0.2	0.2	0.2	0.15	0.2	0.2	0.2	0.2	0.2
Antisheep.........	0.1	0.15	0.1	0.1	0.15	0.2	0.1	0.15	0.2	0.2
*Antisheep.........	0.2	0.2	0.2	0.2	0.2	0.2	0.15	0.2	0.2	0.2

HEMOLYTIC SYSTEM	UNIT OF COMPLEMENT IN C.C. OF UNDILUTED SERA OF 20 PERSONS									
	11	12	13	14	15	16	17	18	19	20
Antihuman........	0.15	0.15	0.2	0.2	0.2	0.15	0.2	0.2	0.2	0.2
Antisheep.........	0.15	0.1	0.2	0.2	0.1	0.1	0.1	0.15	0.1	0.1
*Antisheep.........	0.2	0.1	0.2	0.3	0.2	0.2	0.15	0.2	0.1	0.2

*With removal of natural antisheep hemolysin from each serum.

(a) *Variation in the Hemolytic Activity of Complement Sera of Animals of the Same Species.*—As previously stated, our experiments indicate that the presence of variable amounts of natural hemolysin and agglutinins in complement sera for the corpuscles of the indicator antigen is one source of variation in the hemolytic activity of different sera from animals of the same species; for example, when the natural antisheep hemolysin is absorbed from human complements, the lytic activity is rendered more constant for these sera. In Table XXII are shown the lytic units of 20 human complement sera for sheep cells and after the removal of natural antisheep hemolysin; taking 0.1 c.c. of serum as the unit before removal of the natural hemolysin we found that 50 per cent of the sera contained more or less than this amount of complement, whereas after removal of the hemolysin, the average unit was 0.2 c.c. and but 25 per cent varied from this unit.

TABLE XXIII

VARIATION IN THE HEMOLYTIC ACTIVITY OF GUINEA PIG COMPLEMENT IN AN ANTISHEEP SYSTEM

COMPLEMENT	DOSES OF SERUM DILUTED 1:20					
	0.1 c.c.	0.2 c.c.	0.3 c.c.	0.4 c.c.	0.5 c.c.	0.6 c.c.
No. 1	M.H.[*]	M.H.	H.	H.	H.	H.
No. 2	M.H.	M.H.	H.	H.	H.	H.
No. 3	M.H.	M.H.	H.	H.	H.	H.
No. 4	N.H.	S.H.	S.H.	M.H.	H.	H.
No. 5	N.H.	S.H.	M.H.	H.	H.	H.
No. 6	N.H.	M.H.	H.	H.	H.	H.
[†]Mixture	M.H.	M.H.	H.	H.	H.	H.
No. 7	S.H.	H.	H.	H.	H.	H.
No. 8	S.H.	M.H.	H.	H.	H.	H.
No. 9	S.H.	M.H.	H.	H.	H.	H.
No. 10	N.H.	S.H.	S.H.	M.H.	M.H.	H.
No. 11	S.H.	M.H.	H.	H.	H.	H.
No. 12	N.H.	S.H.	M.H.	M.H.	H.	H.
[‡]Mixture	S.H.	M.H.	H.	H.	H.	H.

[*] H.=complete hemolysis; M.H.=marked hemolysis; S.H.=slight hemolysis; N.H.=no hemolysis.

[†] A mixture of equal parts of sera of pigs 1 to 6 inclusive.

[‡] A mixture of equal parts of sera of pigs 7 to 12 inclusive.

Furthermore, in experiments of this kind it is imperative to collect the complement sera in exactly the same manner and at the same time and to use the same corpuscles in exactly the same dose with exactly the same amount of hemolysin; our tests were conducted in this manner with groups of from six to twenty sera at a time.

Table XXIII shows the results obtained in one experiment conducted with twelve guinea pig sera and is a fair example of the amount of variation found in tests of this character and under these conditions with complements which were *not* absorbed with the corpuscles of the indicator antigen prior to the titration. Tables XXIV and XXV also show the degree of variation in lytic activity for sheep and human cells displayed by the individual complements of persons, guinea pigs, rats, rabbits, sheep, hogs and oxen.

An analysis of our results indicates that in an antihuman hemolytic system about 50 per cent of human complements will vary to some extent from a uniform unit and about 30 per cent of guinea pig complements will show some variation. In an antisheep system about 65 per cent human and 30 per cent guinea pig complements show some variation. These results are presented in Table XXIV; the variations were very slight in the majority of instances and only demonstrable by strict attention to details in the titrations.

TABLE XXIV

VARIATION IN THE HEMOLYTIC ACTIVITY OF THE COMPLEMENTS OF VARIOUS ANIMALS FOR HUMAN AND SHEEP CELLS

COMPLEMENTS	PERCENTAGE OF COMPLEMENTS SHOWING VARIATION	
	In Antisheep System	In Antihuman System
Human	65 per cent	50 per cent
Guinea Pig	30 " "	30 " "
Rat	50 " "	50 " "
Rabbit	60 " "	60 " "
Sheep	not determined	65 " "
Hog	50 per cent	65 " "
Ox	not determined	50 " "

(b) *Variation in the Fixability of Human and Guinea Pig Complement Sera.*—Tests for variation in fixability were conducted after the method of Browning and McKenzie as described briefly above; this method impressed us as being the only accurate means for determining the fixability of a complement. By titrating each complement with an excess of hemolysin, the unit of complement is reduced to a minimum so as to avoid the use of large amounts of complement serum in those tubes calling for five or more units of complement and thereby removing the liability of interference of complement fixation by the deviation of syphilis antibody and antigen by indifferent serum proteins.

TABLE XXV

VARIATION IN THE FIXABILITY OF HUMAN COMPLEMENT IN AN ANTIHUMAN HEMOLYTIC SYSTEM

SERA NO.	HEMOLYTIC UNITS	COMPLEMENT FIXATION SERIES								SERUM CONTROLS			ANTIGEN CONTROLS			UNITS OF COMPLEMENT FIXED
		1	2	3	4	5	6	7	8	1	2	3	1	2	3	
1	0.04	+	+	+	+	+	−	−	−	+	+	−	+	−	−	2
2	0.06	+	+	+	−	−	−	−	−	+	−	−	+	−	−	1
3	0.05	+	+	+	+	+	+	−	−	+	+	−	+	+	−	2
4	0.05	+	+	+	+	−	−	−	−	+	−	−	+	+	−	1
5	0.05	+	+	+	+	+	+	−	−	+	+	−	+	+	−	3
6	0.06	+	+	+	+	−	−	−	−	+	−	−	+	−	−	2
*Mixture	0.05	+	+	+	+	+	−	−	−	+	−	−	+	+	−	2
†Pig	0.04	+	+	+	+	−	−	−	−	+	−	−	+	−	−	2

Heated syphilitic serum used in dose of 0.1 c.c. with five antigenic units of antigen of acetone-insoluble lipoids.

*Mixture of equal parts of sera 1—6.

†A mixture of four guinea pig sera.

TABLE XXVI

VARIATION IN THE FIXABILITY OF GUINEA PIG COMPLEMENT BY SYPHILIS SERUM AND ANTIGEN IN AN ANTISHEEP HEMOLYTIC SYSTEM

COMPLEMENT	HEMOLYTIC UNITS C.C.	FIXATION SERIES						SERUM CONTROLS			ANTIGEN CONTROLS			HEMOLYTIC CONTROLS 1 UNIT	UNITS OF COMPLEMENT FIXED
		1 U.	2 U.	3 U.	4 U.	5 U.	6 U.	1 U.	2 U.	3 U.	1 U.	2 U.	3 U.		
1	.015	++*	++	++	++	+	−	+	−	−	+	−	−	−	3 units
2	.015	++	++	++	++	+	−	+	−	−	+	−	−	−	3 units
3	.015	++	++	++	++	+	−	+	−	−	+	−	−	−	3 units
4	.025	++	++	++	++	+	−	+	−	−	+	−	−	−	3 units
5	.02	++	++	++	++	++	+	+	+	−	+	−	−	−	3 units
6	.015	++	++	++	++	++	+	+	+	−	+	+	−	−	2 units
7	.01	++	++	++	+	−	−	+	−	−	+	−	−	−	2 units
8	.015	++	++	++	+	−	−	+	−	−	+	−	−	−	2 units
9	.015	++	++	++	++	+	−	+	−	−	+	−	−	−	3 units
10	.03	++	++	++	+	−	−	+	−	−	+	−	−	−	2 units
11	.015	++	++	++	++	+	−	+	−	−	+	−	−	−	3 units
12	.025	++	++	++	+	−	−	+	−	−	+	−	−	−	2 units
†Mixture 1	.015	++	++	++	++	++	−	+	−	−	+	−	−	− −	3 units
‡Mixture 2	.015	++	++	++	+	+	−	+	−	−	+	−	−	−	3 units

Heated syphilitic serum used in dose of 0.1 c.c. with five antigenic units of an antigen of acetone-insoluble lipoids.

*++=strongly positive; +=weakly to moderately positive; −=negative.

†Mixture of complements 1—6 inclusive.

‡Mixture of complements 7—12 inclusive.

A large number of experiments have been made with groups of six to twelve complements from guinea pigs and healthy nonsyphilitic persons in each experiment employing the same syphilitic serum, same antigen, same hemolytic system and with rigid attention to technical details in order to render the results strictly comparative. The results of one experiment with human complements is shown in Table XXV and of an experiment with guinea pig complements in Table XXVI. The results are expressed in the units of complement fixed by the positive serum (heated) and antigen after the amount of complement in units fixed by antigen alone and serum alone had been subtracted.

Tests of this character were not conducted with the complements of other animals because no other complement can be seriously considered for a standardized Wassermann test other than human and guinea pig complements.

The general result of these tests has been to indicate (1) that both guinea pig and human complements vary in fixability and (2) that human complements are more apt to show this variation in fixability than guinea pig complement. According to our experiments about 50 per cent of human and about 30 per cent of guinea pig complements show variation in fixability. Doubtless this is a potent factor for error and an explanation in part of the variable results reported by different laboratories testing the same serum and particularly if the serum of one pig is relied upon for furnishing complement.

Part 4

THE INFLUENCE UPON THE RESULTS OF THE WASSERMANN TEST CONDUCTED WITH SINGLE AND MULTIPLE COMPLEMENTS

By reason of this known variation in the fixability of guinea pig complement many serologists, probably a majority of those working in large laboratories, have employed a mixture of complement sera in conducting complement-fixation tests. In smaller laboratories conducting relatively few tests per week single complements are generally employed.

While the advisability of using multiple complements is based upon the results of titrations of guinea pig complements, actual comparative Wassermann tests employing single and mixed complements with a large number of selected sera do not appear to have been reported upon, and we considered the question of sufficient importance to devote considerable time to it. Accordingly 126 selected sera were subjected to the Wassermann test employing three antigens, namely cholesterinized alcoholic extract of human heart, alcoholic extract of syphilitic liver and acetone resoluble lipoids; the results have proved of great interest and brought out several important facts.

In conducting these tests an antisheep hemolytic system was employed with sera heated at 56° C. for one half hour and used in dose of 0.2 c.c. with each antigen. In each experiment twenty sera were tested at one time employing the complement serum of one pig and a mixture of sera of three pigs in the second series. These complements were employed in a constant dose of 1 c.c. of 1:20 dilution (0.05 c.c. undiluted serum), the same hemolysin diluted 1:1000 being titrated against each and employed in the main tests in a dose of two hemolytic units. The results of these hemolysin titrations are shown in Table XXVII; with the mixture of complements the unit of hemolysin was usually smaller than the unit with a single complement.

Table XXVII

The Influence Upon Hemolysin Titrations of Single and Multiple Complements

TITRATIONS	UNIT OF HEMOLYSIN WITH SINGLE COMPLEMENT	UNIT OF HEMOLYSIN WITH MULTIPLE COMPLEMENT
For Sera 1 to 20	0.3 c.c.	0.2 c.c.
For Sera 21-40	0.3 c.c.	0.3 c.c.
For Sera 41-60	0.5 c.c.	0.4 c.c.
For Sera 61-80	0.6 c.c.	0.6 c.c.
For Sera 81-100	0.6 c.c.	0.2 c.c.

Table XXVIII

The Results of Wassermann Tests with the Sera of Sixty Syphilitic Persons Conducted with Single and Multiple Guinea Pig Complements

ANTIGENS	RESULTS OF TESTS EMPLOYING ONE COMPLEMENT		RESULTS OF TESTS EMPLOYING MULTIPLE COMPLEMENT	
	+	—	+	—
Cholesterinized alc. ext.	54	6	58	2
Alc. ext. syph. liver	40	20	41	19
Acetone-insoluble lipoids	53	7	55	5

The results of Wassermann tests with one hundred of these sera are shown in Tables XXVIII and XXIX; the sera were carefully selected as regards clinical expectancy, the syphilitic sera being chosen from patients in the syphilis clinic of Professor Schamberg, and the negative sera largely from assistants and medical students. Twenty-six of the 126 sera proved anticomplementary in the tests with one complement or a mixture of complements, and are not included in the analysis but listed separately in Table XXX.

TABLE XXIX

THE RESULTS OF WASSERMANN TESTS WITH THE SERA OF FORTY NONSYPHILITIC PERSONS CONDUCTED WITH SINGLE AND MULTIPLE GUINEA PIG COMPLEMENTS

ANTIGENS	RESULTS OF TESTS EMPLOYING ONE COMPLEMENT		RESULTS OF TESTS EMPLOYING MULTIPLE COMPLEMENT	
	+	—	+	—
Cholesterinized alc. ext.	3	37	0	40
Alc. ext. syph. liver	1	39	0	40
Aceton insol. lipoids	0	40	0	40

TABLE XXX

THE SERUM CONTROLS OF WASSERMANN TESTS CONDUCTED WITH 126 SERA EMPLOYING SINGLE AND MULTIPLE COMPLEMENTS

RESULTS WITH SINGLE COMPLEMENT		RESULTS WITH MULTIPLE COMPLEMENT	
Partial hemolysis	Comple hemolysis	Partial hemolysis	Complete hemolysis
26	100	6	120

The practical results of these comparative tests may be summarized as follows:

1. A mixture of several complements yields a higher percentage of true positive reactions as shown in Table XXVIII; the results varied with the antigens as was expected, the cholesterinized extract yielding the largest number of positive reactions and the alcoholic extract of syphilitic liver the least.

2. A mixture of several complements is not as apt to yield falsely positive reactions as a single complement, as shown in Table XXIX; of the 40 sera of normal healthy persons tested the cholesterinized extract yielded three and the alcoholic extract of syphilitic liver one weakly positive reaction in the tests conducted with one complement whereas with the mixture of complements all tests were clearly negative. In other words *a single complement is more susceptible to non-*

specific fixation or the anticomplementary action of antigen than a mixture of complements and this may have a bearing upon the unfavorable reports of several serologists in reference to cholesterinized extracts yielding falsely positive results. This observation is supported by the following:

3. A mixture of complements is not as susceptible to the anticomplementary action of serum as a single complement (Table XXX); of the 126 sera studied, 26 were anticomplementary in tests employing one complement, while only 6 of these were anticomplementary with the mixture of complements. In no instance was a serum anticomplementary with the mixture of complements alone; in other words *some complements are more susceptible than others to anticomplementary influences and in a mixture of several this tendency is reduced to a minimum.*

Part 5

THE INFLUENCE OF THE METHOD OF PREPARATION UPON THE HEMOLYTIC ACTIVITY AND FIXABILITY OF GUINEA PIG AND HUMAN COMPLEMENTS

Various methods are employed in different laboratories for the collection and preparation of guinea pig complement serum. For example, in some laboratories the animals are bled the day before and the serum allowed to separate in the laboratory or in the refrigerator; in others the animals are bled on the day the serum is required, one or several hours before being used. A question of practical importance is whether or not the lytic activity and fixability of a serum is influenced by the method of collection.

Browning and McKenzie[17] found that freshly drawn serum is hypersensitive to the anticomplementary activity of antigen alone and patient's serum alone and advocate keeping a serum on ice for eighteen to twenty-four hours before use; Gurd[18] found that guinea pig and human complement sera gradually increased in activity if kept for an hour in the incubator and then in the refrigerator, when they would remain constant for twenty-four to forty-eight hours followed by deterioration. Noguchi and Bronfenbrenner[13] found that guinea pig sera left in contact with the clot for forty-six hours were usually more active than after twenty-four hours (a few became weaker), and that to insure greater uniformity it was preferable to let sera remain in the clots for at least twenty-four hours before use. These investigators also found that variation in fixability was more marked than variation in lytic activity under the condition of their experiments.

Hemolytic Complement and Antibodies in Plasma.—Of primary importance in this connection is whether or not complements exist preformed in plasma; Gengou[19] originally claimed that they did not but developed only upon the production of serum after coagulation had taken place. Considerable work has since been conducted on this problem with conflicting results; recently Watanabe[20] working in these laboratories, perfected a method for the collection of plasma which proved generally satisfactory and in a series of very carefully executed experiments demonstrated the presence of hemolytic complement in the sera of persons and the lower animals in amounts closely similar to the corresponding sera and likewise the presence of such antibodies as hemolysins, agglutinins and the antibody concerned in the Wassermann reaction.

Our experiments were conducted with guinea pig and human complements and consisted in collecting and dividing each specimen into five or six equal parts in small sterile centrifuge tubes. *One* part was broken up at once with a glass rod and centrifuged for the serum. A *second* part was placed in an incubator at 38° C. for one hour, broken up and centrifuged. A *third* part was placed in the incubator for an hour and then in a refrigerator for twenty-four hours; if the serum had not separated thoroughly the coagulum of blood was gently broken up and centrifuged. A *fourth* part was allowed to separate at room temperature requiring generally five or six hours. A *fifth* part was placed in the refrigerator for twenty hours and a *sixth* for forty-eight hours.

Each specimen was then titrated for hemolytic activity with the same dose of hemolysin and same dose of the same corpuscle suspension; in this manner an attempt was made to make the tests rigidly comparative for the five or six parts of each specimen. In the fixation tests the same syphilitic serum and same antigen were employed in a technic previously mentioned and consisting in measuring the fixability of each complement according to the number of units of complement fixed by antigen alone, serum alone, and in mixtures of serum and antigen as shown in Table XXXIII.

A large number of guinea pig and human complements were tested in this manner in an antisheep and antihuman hemolytic system; the results of several experiments are shown in Tables XXXI, XXXII, and XXXIII.

Table XXXI

The Influence of the Method of Preparation Upon the Hemolytic Activity and Fixability of Guinea Pig Complement in an Antisheep Hemolytic System

A. Blood defibrinated at once and centrifuged for serum.

B. Blood placed in incubator for one hour; clot broken up and centrifuged.

C. Blood kept at room temperature for about 6 hours and serum separated.

D. Blood kept in refrigerator at -2° C. for 18 to 24 hours and centrifuged.

E. Blood kept in refrigerator at -2° C. for 48 hours and centrifuged.

GUINEA PIG	HEMOLYTIC UNIT OF COMPLEMENT IN C.C. UNDILUTED SERUM				
	Method A	Method B	Method C	Method D	Method E
No. 1	0.035	0.03	0.025	0.035	0.04
No. 2	0.035	0.04	0.03	0.03	0.05
No. 3	0.028	0.02	0.028	0.028	0.03
No. 4	0.035	0.03	0.03	0.03	0.035
No. 5	0.02	0.02	0.015	0.02	0.02
No. 6	0.02	0.015	0.025	0.03	0.03
No. 7	0.02	0.02	0.035	0.03	0.03
No. 8	0.03	0.025	0.025	0.03	0.03
No. 9	0.02	0.02	0.015	0.02	0.02
No. 10	0.03	0.02	0.025	0.03	0.03
No. 11	0.035	0.035	0.	0.04	0.04
No. 12	0.035	0.035	0.025	0.035	0.035
	COMPLEMENT FIXED BY SYPHILITIC SERUM AND ANTIGEN				
No. 1	3 units	3 units	4 units	4 units	4 units
No. 2	2 “	3 “	2 “	3 “	4 “
No. 3	3 “	4 “	4 “	3 “	4 “
No. 4	3 “	3 “	4 “	4 “	4 “
No. 5	2 “	2 “	3 “	4 “	4 “
No. 6	2 “	3 “	3 “	4 “	4 “
No. 7	3 “	3 “	4 “	4 “	5 “
No. 8	3 “	4 “	4 “	4 “	4 “
No. 9	2 “	3 “	4 “	4 “	5 “
No. 10	3 “	3 “	3 “	3 “	4 “
No. 11	4 “	4 “	4 “	5 “	5 “
No. 12	3 “	3 “	3 “	4 “	4 “

Table XXXII

The Influence of the Method of Preparation upon the Hemolytic Activity and Fixability of Human Complement in an Antisheep Hemolytic System

A. Blood defibrinated at once and centrifuged for serum.

B. Blood placed in incubator for one hour; clot broken up and centrifuged.

C. Blood placed in incubator for one hour and in refrigerator for 23 hours.

D. Blood kept in laboratory at about 74° F. for five hours.

E. Blood kept in refrigerator at $-2°$ C. for 24 hours.

F. Blood kept in refrigerator at $-2°$ C. for 48 hours.

SERUM	HEMOLYTIC UNIT OF COMPLEMENT IN C.C. UNDILUTED SERUM					
	Method A	Method B	Method C	Method D	Method E	Method F
No. 1	0.037	0.017	0.037	0.022	0.037	0.037
No. 2	0.037	0.02	0.02	0.022	0.025	0.037
No. 3	0.02	0.017	0.025	0.02	0.02	0.025
No. 4	0.02	0.017	0.02	0.02	0.025	0.037
No. 5	0.037	0.02	0.037	0.037	0.037	0.04
No. 6	0.02	0.017	0.02	0.025	0.025	0.037
	COMPLEMENT FIXED BY SYPHILITIC SERUM AND ANTIGEN					
No. 1	3 units	4 units	4 units	4 units	4 units	4 units
No. 2	2 “	2 “	4 “	4 “	2 “	3 “
No. 3	4 “	5 “	3 “	4 “	4 “	4 “
No. 4	3 “	4 “	4 “	4 “	5 “	5 “
No. 5	2 “	3 “	3 “	3 “	2 “	3 “
No. 6	3 “	4 “	4 “	4 “	4 “	4 “

Table XXXIII

The Influence of the Method of Preparation upon the Fixability of Human Complement in an Antisheep Hemolytic System

METHOD OF PREPARATION	FIXATION SERIES							SERUM CONTROLS			ANTIGEN CONTROLS			HEMOLYTIC CONTROLS		UNITS FIXED
	2 U.	3 U.	4 U.	5 U.	6 U.	7 U.	8 U.	1 U.	2 U.	3 U.	1 U.	2 U.	3 U.	1 U.	3 U.	
Serum secured at once	++	++	++	++	—	—	—	++	—	—	++	—	—	—	—	3
Blood in incubator one hour	++	++	++	++	++	+	—	++	—	—	++	—	—	—	—	5
Blood in incubator one hour; refrigerator 23	++	++	++	+	—	—	—	++	—	—	+	—	—	—	—	3
Blood at room temperature 5 hours	++	++	++	++	++	+	—	++	—	—	++	—	—	—	—	5
Blood in refrigerator 24 hours	++	++	++	+	+	—	—	++	—	—	++	—	—	+	—	3
Blood in refrigerator 48 hours	++	++	++	++	+	—	—	++	—	—	++	..	—	+	—	3

The results of our experiments may be summarized as follows:

1. With the methods employed variations in hemolytic activity and fixability were slight and inconstant.

2. As a general rule, complement secured by defibrinating the blood immediately after collection and centrifuging for the serum was slightly inferior in hemolytic activity and fixability and occasionally hypersensitive to the anticomplementary influence of antigen alone and serum alone, as stated by Browning and McKenzie.

3. Complement secured by placing the blood in the incubator for an hour before breaking up and centrifuging the clot generally acquired an increase of lytic activity and fixability as stated by Gurd; for example a guinea pig complement proving completely lytic in 0.03 c.c. secured immediately after bleeding would be lytic in 0.025 c.c. when secured from a portion of the same blood placed in the incubator for an hour before centrifuging. With human complement the same differences were frequently noted and usually in a slightly greater degree.

4. Complement serum which separated from clots at room temperature over a period of six to twelve hours generally possessed a degree of lytic activity and fixability as good as yielded by any method.

5. Blood placed in the refrigerator immediately after collection and the temperature rapidly reduced to -2° C. and kept for eighteen to twenty-four hours generally yielded a complement serum of reduced lytic activity although fixability was not influenced. After forty-eight hours the lytic activity was the same or slightly decreased and fixability apparently increased due to increased sensitiveness of the complement to antigen alone and serum alone which yielded reaction suggestive of possible increased fixability of complement but not an actual or absolute increase.

Part 6

THE INFLUENCE OF AGE, SEX, HEALTH, DIET, REPEATED BLEEDINGS AND ANESTHESIA OF GUINEA PIGS UPON THE PROPERTIES OF COMPLEMENT

We have been unable to find reports in literature bearing upon this subject beyond isolated statements of several authors that complement derived from sickly animals or from persons suffering from febrile diseases is apt to be poor in hemolytic activity. The question, however, of the possible influence of age, sex (pregnancy), general health, feeding, repeated bleedings and anesthesia of guinea pigs in relation to the properties of their complement insofar as complement fixation is concerned, has been considered worthy of special study.

(a) *Influence of Age.*—The sera of twelve guinea pigs weighing from 200 to 280 grams compared with the sera of twelve weighing from 400 to 580 grams showed no variation in hemolytic activity, and fixability beyond those variations possible and to be expected due to individual differences. These animals were taken from the same pens, received the same food and were bled at the same time and the sera collected in the same manner, that is, each specimen was placed in the incubator for one hour followed by breaking up of the clots and centrifuging for the sera which were tested at once for hemolytic activity and fixability. Sera from *younger pigs were frequently poorer in hemolytic activity and more sensitive to the anticomplementary activity of antigen alone and serum alone; large heavy animals are always most likely to yield complements of remarkably uniform lytic activity and fixability and should always be preferred.*

(b) *Influence of Sex (Pregnancy).*—Sera from bloods secured from the hearts of sixteen pregnant pigs weighing over 450 grams compared with sera collected at the same time and in the same manner from males of corresponding weight and living under identical conditions, showed no constant changes in hemolytic activity and fixability. Occasionally sera collected near term and within twenty-four hours after delivery were poorer in hemolytic activity and somewhat hypersensitive to the anticomplementary influence of antigen alone and serum alone.

(c) *Influence of General Health.*—Experiments with groups of pigs weighing from 200 to 300 grams suffering with generalized tuberculosis of over fourteen days' duration or within one to three weeks after injection with diphtheria toxin or cultures of the diphtheria bacillus as the survivors of tests for toxicity and virulence, have shown with fair uniformity that the complements are below the average in hemolytic activity and quite hypersensitive to the anticomplementary action of antigen alone and serum alone; *any guinea pig that is thin and wasted from these or other causes is so apt to yield an unsatisfactory complement serum that they should not be used.* On the other hand, pigs surviving injections of diphtheria and tetanus toxins and antitoxins given some months previous, in good general health and of approximately normal weight are entirely likely to yield acceptable complement sera; in our experience however, a large number of these animals remain undersized and undernourished and frequently yield unsatisfactory complement sera.

(d) *Influence of Diet.*—The influence of diet upon the properties of complement is difficult for us to evaluate in the absence of systematized and scientifically regulated diet experiments; our animals were given a mixed diet of uncooked vegetables and grains (principally oats) according to the season of the year and among those animals of good health and normal weight we have never noted any constant changes in the properties of complement except on two occasions when pigs fed on cabbage for several weeks with occasional meals of carrots or beets, yielded complements poor in hemolytic activity and quite sensitive to the anticomplementary influences of serum and antigen. This subject is worthy of systematized study because of its general import; *insofar as complement for Wassermann tests is concerned, mixed diet maintaining the animals in good health and of normal weight is all that is required.*

Of equal interest and importance in this connection is the influence of feeding upon the properties of complement. We have removed two cubic centimeters of blood from the jugular veins or hearts of a series of large animals after starvation for twenty-four hours and again after a meal of vegetables and oats and compared the two sera of each animal for hemolytic activity and fixability with the general result that the sera of the first bleeding, that is, from starved or rather hungry animals, was superior in lytic activity and fixability to sera removed within an hour after feeding and frequently chylous in appearance. For this reason it appears advisable to regulate the time of feeding in such manner that animals are bled for Wassermann tests at least six hours after feeding.

(e) *Influence of Repeated Bleedings.*—Now that it is a growing custom in laboratories to bleed guinea pigs from the heart or jugular veins in order to secure small quantities of blood from several animals without killing them, to meet the requirements of using a mixture of complement sera and for purposes of economy, a question of importance concerns the possible influence of repeated bleedings upon the properties of complement. The experiments which we have conducted have shown remarkably little influence on the lytic activity and fixability of complements from pigs bled profusely at intervals of one week (about 15 c.c. of blood from 500-600 gram animals) or of smaller bleedings at intervals of ten days to two weeks. In four animals surviving eight large bleedings at intervals of five days an anemia was produced and these sera were finally distinctly below the average in lytic activity although comparatively unchanged in fixability.

Insofar as we can judge, healthy adult guinea pigs may be bled once every two or three weeks in the proportion of 1 c.c. of blood per 100 grams of body weight without deleterious influence upon the qualities of their complements.

(f) *Influence of Anesthesia.*—The brief anesthesia (five to ten minutes) with ether required for bleeding a guinea pig does not appear to influence the properties of the complement; blood removed from twelve adult pigs before and after a fifteen-minute period of ether anesthesia yielded complements of closely similar hemolytic activity and fixability.

Part 7

A METHOD FOR THE COLLECTION OF COMPLEMENT SERUM

Aside from the questions concerning what serum is best adapted for complement in a standardized Wassermann reaction and the best methods for titrating and using it which are discussed elsewhere (2, 3), it would appear advisable to describe a technic which we have built up on the basis of results of tests and experience described in this paper, and found very satisfactory for routine use.

The following review of methods employed by various serologists is helpful in this connection.

Neill[21] in a description of the technic employed in the Hygienic Laboratory states: "Bleed not less than five full-grown guinea pigs from the heart by means of a sterile syringe, previously rinsed with salt solution. With proper technic, from 5 to 10 c.c. may be obtained without injury to the animal. Pigs may be kept for this purpose and bled once in two weeks. Place the blood drawn from each pig in a separate centrifuge tube, and allow to clot. Separate the clot from the side of the tubes with sterile needle or pipette and place in 37° C. water-bath for one hour. Then place in cold box overnight, or, if serum has separated, pipette the serum immediately. Centrifuge clear of red blood corpuscles and pool the sera in a sterile glass container."

Craig[22] uses the following method which is identical with that employed by Vedder and widely employed in the army laboratories; two or three guinea pigs are bled from the heart or to death from the vessels of the throat and "the blood ejected into a sterile Petri dish, allowed to stand at room temperature for two hours and then placed in the ice box overnight."

Noguchi[23] selects large animals and bleeds from the carotid artery into a large Petri dish. The dish is then covered and left at room temperature for a few hours for the clot to form and the serum to separate. The separation of the serum is completed in the refrigerator requiring from five to ten hours.

Browning and McKenzie[17] describe their technic as follows: "The hair of the animal's neck is cut or shaved, and after cleansing with a pad of cotton wool moistened with salt solution, the blood is obtained by cutting the vessels transversely with a single sweep of a very sharp knife; it is collected in a sterile glass cylinder, into the mouth of which the narrow end of a sterile glass funnel dips. The wide end of the funnel should be about 7 to 10 inches in diameter; it serves to catch the blood flowing from the severed vessels. The clot must usually be separated from the sides of the glass, which should have been previously washed out with sterile normal saline solution. The serum is allowed to separate for eighteen to twenty-four hours at room temperature, and is then pipetted off."

Park and Williams[24] describe the following method in use in the New York Department of Health: "The pigs after being stunned by a blow at the base of the skull, are bled from the throat with due care against cutting the esophagus, as the stomach contents might render the serum unfit, into Petri dishes, which are kept at room temperature until the serum begins to separate and then set in the ice box for several hours. The serum is drawn off with a capillary pipette and centrifuged if not free from blood cells."

Thomas and Ivy[25] etherize a full-grown guinea pig by placing its head in a glass containing gauze soaked with ether, and before death occurs the blood vessels of the neck are severed and the blood collected in a Petri dish. The blood is allowed to coagulate (presumably at room temperature) and the clear serum to separate, which it does in about two hours.

Standardized Technic.—1. For guinea pig complement select large well-nourished animals which have not been fed within twelve to twenty-four hours of the time for bleeding; avoid pregnant animals.

2. Collect blood in a *chemically clean* and preferably sterile centrifuge tube by means of a clean funnel about 4 inches in diameter, or in a Petri dish. We prefer the former because if separation of serum is unsatisfactory the clot may be gently broken up with a glass rod and the serum secured by centrifuging the material. Chemical cleanliness is essential because traces of acids or alkalies are destructive of complement.

3. If guinea pigs are to be bled to death, stunning the animals with a blow at the base of the skull is preferable to ether and chloroform anesthesia because cardiac activity is not interfered with and the maximum amount of blood is obtained. Guinea pigs may also be bled from the ears without anesthesia; or from the heart or an external jugular vein under light ether anesthesia.

4. In bleeding a guinea pig to death it is not necessary to shave the neck; a few hairs in the blood do not alter the properties of the serum. The great vessels on one or both sides should be *quickly* severed and preferably with a pair of stout sharp scissors with one pointed blade to facilitate piercing of the skin and underlying tissues. It is easy to avoid cutting the trachea and esophagus, but it does not appear to make any difference whether the trachea is cut; the esophagus should not be cut because in squeezing the abdomen to pump out blood in the great vessels stomach contents may escape although even this accident is rare in our experience.

5. In bleeding from the heart a chemically clean and sterilized 5-10 c.c. all glass or glass-metal syringe fitted with a short needle of about gauge 20 may be used; in bleeding from an external jugular vein the hairs are plucked just above the region of the clavicle and a small incision made through the skin and vein with collection of blood by means of a funnel into centrifuge tubes. As soon as the animal is released, bleeding ceases and the wound heals promptly and without infection.

6. *Do not use the blood immediately after bleeding;* if the animals are bled on the day the serum is to be used, place the clots in the incubator at 37° C. for an hour followed by breaking up each with a glass rod and centrifuging, or let the clots stand at room temperature for two or three hours for separation of serum which if not

complete may be finished by centrifuging. Animals may be bled late in the afternoon of the day before and the clots placed in the incubator for one hour or left at room temperature for two hours and then placed in a refrigerator until the following day. If the sera have separated but poorly, gently break up the clots and centrifuge. *It is preferable to leave the serum on the clot in the refrigerator until ready for use; unused serum should be returned to the refrigerator until required.* Traces of hemoglobin in the serum do not interfere, but the serum should be free of corpuscles.

7. Human complement to be used for activating an inactive serum is collected by aspirating blood from a healthy nonsyphilitic person in a sterile syringe from a vein at the elbow after cleansing of the skin; the specimen should be placed in an incubator for one hour or left at room temperature for at least two hours followed by gentle breaking up of the clot and centrifuging for the clear corpuscle free serum.

8. To remove a natural agglutinin or hemolysin for the erythrocytes of a particular animal from a complement serum, the serum should be chilled in a mixture of ice and salt and 0.1 c.c. of thoroughly washed corpuscles added for each cubic centimeter of serum, mixed and allowed to remain at a low temperature to inhibit complement activity for at least an hour followed by rapid and brief centrifugalization for corpuscle-free serum.

SUMMARY

1. The complement serums employed in the Wassermann test should be suitable for the hemolytic system, that is, free of agglutinin and hemolysin for the cells of the indicator antigen. The presence of agglutinin may interfere with hemolysis and is more important in this connection than the presence of natural hemolysin.

2. Guinea pig serum complement being practically free of agglutinins for the erythrocytes of persons, guinea pigs, sheep, oxen and chickens is adapted to any hemolytic system employing these cells; human serum complement contains agglutinins for these cells but least for ox cells and next in order for the erythrocytes of the chicken, sheep, guinea pig, and human.

3. The agglutinins in human sera for the erythrocytes of various animals show grouping, as is well known of the agglutinin for human cells.

4. The complement serum for the Wassermann test must possess a high degree of hemolytic activity for the erythrocytes of the indicator antigen; a study of the complements of persons, guinea pigs, rats, rabbits, sheep, hogs, and oxen in antisheep, antiox and antihuman hemolytic systems have shown that guinea pig complement is most active and particularly in an antisheep system. Human complement is from six to seven times weaker.

5. The complement serum for the Wassermann test must be highly sensitive to fixation by syphilis antibody and organ extracts; mixtures of human complements were generally most sensitive of those studied with guinea pig complements a close second and rat complement third.

6. The complement serum should be relatively nonsusceptible to the anticomplementary influences of patient's serum alone and antigen alone; guinea pig complement was found least susceptible to these influences.

7. The complements of all animals studied showed variation in hemolytic activity, but guinea pig complements do not vary as much in hemolytic activity for sheep and human erythrocytes as human complements.

8. All complements likewise showed variation in fixability and human complement was found to show more variation than guinea pig complement.

9. Owing to variation in hemolytic activity and fixability, a mixture of complements from at least three animals should always be used for furnishing the complement serum in the Wassermann test.

10. Comparative Wassermann tests employing single and mixed complements of guinea pigs have shown that tests conducted with the mixed complements yielded the highest percentage of true positive reactions, was least susceptible to the anticomplementary influences of antigen alone and patient's serum alone and yielded no falsely positive reactions with cholesterinized extracts.

11. The method employed for the collection of complement serum has some influence upon the hemolytic activity and fixability; blood should be placed in the incubator for one hour or allowed to remain at room temperature for at least two hours before the serum is separated.

12. Age, pregnancy, general health, diet and repeated bleedings have some influence upon the properties of guinea pig complement as

discussed in the paper; large, healthy and nonpregnant animals should be chosen for complement from twelve to twenty-four hours after feeding. A method for the collection of complement serum is described.

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THE INTENSIVE TREATMENT OF WOMEN WITH ARSENOBENZOL (SCHAMBERG)*

PROCEDURE AND RESULTS AT THE HOSPITAL JAIL OF SAN JUAN PORTO RICO

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(Received for publication, June 9, 1919)

THE urgent necessity of rendering innocuous a number of women who were likely to be centers of syphilitic infection made it possible to use the intensive application of arsphenamine, as suggested by Pollitzer.

Two classes of cases are reported. The first and most important is a group in which the lesions of syphilis were present about the genitals and the Wassermann was four-plus. There were fifteen women in this class; ten with condylomata lata; two with chancre; one with mucous patches and ulcers of the cervix; one with incised and ulcerating inguinal glands; and one with macular papular secondaries.

The second group of cases were seven women who presented no lesions of syphilis, but whose Wassermann reaction was four-plus. The youth of these made it evident that the syphilitic infections were comparatively recent, and it was deemed advisable to give them arsphenamine in the hope of preventing recurrences.

The plan of treatment was on lines laid down by S. Pollitzer in discussions at dermatologic meetings, in personal conversations, and before the fortieth annual meeting of the American Dermatological Association (J. C. D., September, 1916). This plan is termed the "intensive" method in distinction to the "intermittent" method which is better known. The intensive method as used by us consists of the daily administration intravenously of arsphenamine for three doses. The dose for women is three decigrams of arsenobenzol of Schamberg, dissolved in 50 c.c. of freshly distilled and boiled water, neutralized with 15 per cent of sodium hydroxide. (Reference: Goodman; Preparation of Solutions of Salvarsan and Arsenobenzol for Intravenous Use, New York Med. Jour., June 15, 1918).

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CASE NO.	COLOR	AGE	LESION	1ST. WASSERMANN	ARSPHENAMINE	MERCURY SAL	2ND. WASSERMANN	RESULT
107	White	19	Condylomata lata	Oct. 1, 1918 Four-plus	Oct. 5, 6, 7, Nov. 18, 19, 20	Oct. 4, 11, 16, 22, 28 Nov. 18, 19, 20	Dec. 6, 1918 Three-plus	Lesions all healed. Serology not much affected.
105	Mulatto	18	Condylomata lata	Oct. 1, 1918 Four-plus	Oct. 5, 6, 7,	Oct. 4, 11, 16, 22, 28 Nov. 4	Dec. 6, 1918 Three-plus	Lesions entirely well. Second series not given to this case because of influenza.
43	Mulatto	17	Condylomata lata	Oct. 1, 1918 Four-plus	Oct. 5, 6, 7, Nov. 18, 19, 20	Oct. 4, 11, 16, 22 28 Nov. 4	Dec. 6, 1918 Four-plus	Lesions all healed. Wassermann persists.
106	White	21	Condylomata lata	Oct. 1, 1918 Four-plus	Oct. 5, 6, 7, Nov. 18, 19, 20	Oct. 4, 11, 16, 22, 28 Nov. 4	Dec. 6, 1918 Four-plus	Lesions all well. Persistent positive Wassermann.
51	White	18	Condylomata lata	Oct 16, 1918 Four-plus	Oct. 21, 22 Nov. 18, 19, 20	Oct. 15, 22, 28 Nov. 4	Dec. 6, 1918 Four-plus	Lesions all well. Persistent Wassermann. Third injection of first series omitted by oversight.
61	White	34	No lesions	Oct. 16, 1918 Four-plus	Nov. 18, 19, 20	Oct. 15, 22, 28 Nov. 4	Dec. 6, 1918 Negative	Serological reversal.
37	White	25	No lesions	Oct. 16, 1918 Four-plus	Nov. 18, 19, 20	Oct. 15, 22, 28 Nov. 4	Dec. 6, 1918 Negative	Wassermann reversed.
54	Mulatto	30	No lesions	Oct. 16, 1918 Four-plus	Nov. 18, 19, 20	Oct. 15, 22, 28 Nov. 4	Dec. 6, 1918 Negative	Wassermann reversed.
60	White	18	No lesions	Oct. 16, 1918 Four-plus	Nov. 18, 19, 20	Oct. 15, 22, 28 Nov. 4	Dec. 6, 1918 Two-plus	Wassermann slightly reduced.
66	Negress	25	No lesions	Oct. 16, 1918 Four-plus	Nov. 18, 19, 20	Oct. 15, 22, 28 Nov. 4	Dec. 6, 1918 Four-plus	No change.
79	Negress	35	No lesions	Oct. 16, 1918 Three-plus	Nov. 18, 19, 20	Oct. 15, 22, 28 Nov. 4	Dec. 6, 1918 Four-plus	No change except from three- to four-plus Wassermann.
2	White	18	No lesions	Oct. 16, 1918 Four-plus	Nov. 18, 19, 20	Oct. 15, 22, 28 Nov. 4		Discharged prior to second Wassermann.

CASE NO.	COLOR	AGE	LESION	1ST. WASSERMANN		ARSPHENAMINE	MERCURY SAL	2ND WASSERMANN	RESULT
101	Mulatto	19	Chancre of labia majora	Oct. 16, 1918	Four-plus	Oct. 17, 18, 19 Nov. 18, 19, 20	Oct. 22, 28 Nov. 4	Dec. 6, 1918 Negative	Lesions entirely healed after third injection.
142	White	22	Chancre of labia majora	Oct. 16, 1918	Four-plus	Nov. 18, 19, 20	Oct. 28 Nov. 4	Dec. 6, 1918 Four-plus	Lesion entirely healed. Serology not encouraging
501	White	30	Ulcers of cervix	Oct. 16, 1918	Four-plus	Oct. 17, 18, 19	Oct. 15, 22, 28 Nov. 4	Left before 2nd Wassermann was taken	Lesion entirely healed.
100	White	18	Incised and ulcerating inguinal glands	Oct. 16, 1918	Four-plus	Oct. 17, 18, 19	Oct. 15, 22, 28 Nov. 4	Dec. 6, 1918 Four-plus	Lesions stop ulcerating immediately after 3rd injection. Union within one week.
140	White	23	Papular secondary; legs and arms	Oct. 15, 1918	Four-plus	Oct. 21, 22, 23	Oct. 28 Nov. 4	Dec. 6, 1918 Four-plus	Lesions improved immediately. Disappeared after tenth day.
75	White	25	Generalized macular secondary. Condylomata lata extensive	Oct. 1, 1918	Four-plus	Oct. 5, 6, 7, Nov. 18, 19, 20	Oct. 4, 11, 16, 22, 28 Nov. 4	Dec. 6, 1918 Negative	Condylomata disappeared after third injection. Skin lesion persists for two weeks. Entirely free now. Serology assuring.
105	Mulatto	25	Condylomata lata	Oct. 15, 1918	Four-plus	Oct. 21, 22 Nov. 18, 19, 20	Oct. 15, 22, 28 Nov. 4	Dec. 6, 1918 Negative	Lesions entirely well. Omitted third injection of first series because patient had eaten. Serology assuring.
108	White	26	Condylomata lata	Oct. 16, 1918	Four-plus	Oct. 17, 18, 19 Nov. 18, 19, 20	Oct. 15, 22, 28 Nov. 4	Dec. 6, 1918 Negative	Lesions entirely well after first series of infections. Reversal of Wassermann.
102	White	22	Condylomata lata	Oct. 16, 1918	Four-plus	Oct. 17, 18, 19 Nov. 18, 19, 20	Oct. 15, 22 Nov. 4	Dec. 6, 1918 Negative	Lesions all healed. Wassermann reversed.
301	Negress	19	Condylomata lata	Oct. 16, 1918	Four-plus	Oct. 17, 18, 19 Nov. 18, 19, 20	Oct. 15, 22, 28 Nov. 4	Dec. 6, 1918 Negative	Lesions all healed. Wassermann reversed.

This mode of treatment is a desirable variant of the therapia sterilisans magna of Ehrlich. The theoretic reason for the failure of the latter is that the single dose kills a large number of spirochetes but that some escape and later multiply, become as numerous as before, sensitized to arsenic, and hence more dangerous. Another reason is that the excretion of arsphenamine is begun almost as soon as injected and that in the first few hours most of the drug is out of the body. The intensive method counteracts both these undesirable features because the concentration of the arsenic product in the blood is kept at an efficient, high level for a longer time.

The only figures we have access to are those in Wolbarst's translation, "The Treatment of Syphilis with Salvarsan" by Wechselmann (Rebman and Co. 1911, p. 85).

> "After the intravenous injection, arsenic was eliminated much more rapidly and completely than after the subcutaneous method.
>
> Paralytics given 0.3 gm. intravenously:
> First day........0.0072 gm. arsenic was found.
> Second day.......0.0792 " " " "
> Third day.......0.0053 " " " "
> Fourth day......negative.
>
> Investigations in other patients showed the same results; the excretion of arsenic having been completed within two or three days."

Since arsphenamine is essentially 30 per cent of arsenic it appears that injected intravenously, 90 per cent is excreted by the kidneys in the first two or three days. We were at this time unable to repeat any of the quantitative arsenic determination either in the blood or urine or to undertake the newer fields of arsenic in the spinal fluid following this intensive mode of therapy.

All except two of the women received the preparatory grain of mercury salicylate intramuscularly prior to the first arsphenamine injection. Catharsis was given the night before, and all were on limited diet of milk, soup, and bread for the three day period. Water was given freely. Not a few complained of hunger, which is to be expected. Reactions, immediate or remote to the time of injection, there were none. We attribute this entirely to the care taken in the preparation of the solutions, the dilution, and the care of the patients. Immediately after receiving the injection, the woman was put to bed and kept there for four hours. After that, staying in bed was optional, but they were kept quiet and in the open air.

The clinical results were astounding. Syphilitic lesions disappear within a few days and the patient is no longer a menace. Chancres and condylomata lata are most readily overcome. Mucous patches and skin lesions are next amenable. In other words, infectious lesions are soon destroyed, which is a most important factor in the prevention of community syphilis.

We were not willing, however, to permit the patients' future to rest with a single ''three day dose'' trial, so that cases which had had infectious lesions and were under observation six weeks later were given a second session. Mercury salicylate in grain doses intramuscularly was given weekly.

The Wassermann reaction was repeated on all patients and about half the cases gave a complete reversal from positive to negative. It is far too early though to speak of permanent results.

The therapeutic measures and results are recorded in the accompanying table for all the cases. Fuller histories, social data, and results of using neodiarsenol in a similar manner are being reserved for a fuller report later.

The serologic reactions were performed at the Institute of Tropical Medicine and Hygiene, San Juan, P. R., and were controlled clinically.

ANAL CHANCRE RESULTING FROM PEDERASTY

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REPORTS of extragenital chancres occur far too frequently in the literature for the usual case to deserve any special mention. It was only after being convinced of the few recorded parallels of the case forming the material of this report, that this description was attempted together with a brief review of the literature, which seemed to emphasize the surprising rarity of this mode of infection. It is interesting to note that this condition is more frequently observed in foreign clinics than in this country. Fournier[1] in 1897 called attention to a series of 77 cases of anal chancre, the majority of which were the result of pederasty. Von During[2] from his clinic reported 31 in 1891 with histories similar to the above, and Bubrenilk[3] reported 2 cases in 1909. Occasional cases are described by American observers. Jost and Gradwohl[4] in 1916, Hartley[5] in 1891, and Van Buren[6] each described one case of such infection. Dumesnil[7] in 1900 and Jones[8] in 1917 reported two cases, and Montgomery[9] and Gaskill[10] each observed in their practices three such cases. Bulkley[11] from various clinics collected 87 cases of anal chancre and only one of these from America. 208+1.

It has seemed therefore that a case of anal chancre, and one in which a candid history of pederasty was admitted, might deserve a brief report and a resume of the literature dealing with this type of infection.

The patient G. R. presents himself at the University Hospital on March 29, 1919. He is 17 years of age, of Scotch descent, and by occupation an office boy. In his physique, manner, and general make-up there is a suggestion of the feminine type.

Chief Complaint.—Profuse eruption over the entire body and a painful lesion of the anus.

Family History.—Father died of pneumonia, mother living and well. Two brothers and one sister living, one sister and two brothers died in infancy. One paternal uncle had epileptic "attacks."

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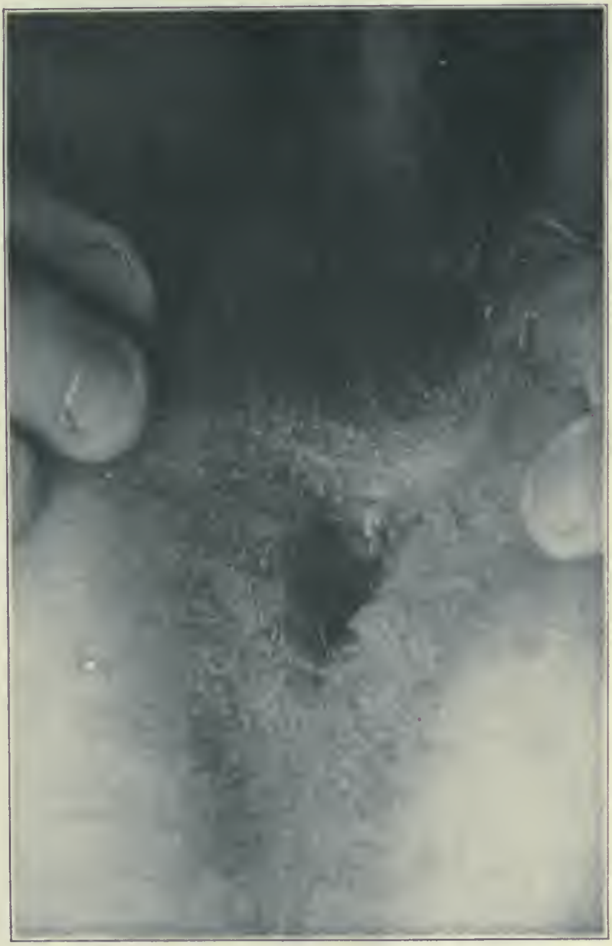

Fig. 1.—Anal Chancre.

Past History.—Except for ''nervousness'' patient has always been well.

Present Illness.—About December 1, 1918, patient was stopped on his way home at night by a man and forced by threat to kill to consent to passive pederasty. Five weeks later he first noticed pain together with a slight hemorrhage on defecation, which has increased in severity until the pain is almost unbearable. Six weeks later an eruption appeared over the entire body. He presented himself to his doctor, being more alarmed at the bleeding from his anus than at the skin rash, and the condition was recognized. Severe nocturnal headaches and pain through the abdomen have been prominent symptoms. During these few months he has lost about twenty pounds in weight.

Examination.—The patient is a rather poorly nourished young man of poor appearance. The scalp is clean. The pupils react to light and in accommodation; the extraocular muscles are normal. The mucous membrane of the mouth is clean. There is a general lymphadenitis, the nodes being characterized as ''shotty.'' Distributed over the entire body including the face, palms, and soles is an erythematous, maculopapular eruption, the lesions being dull red in color and averaging the size of a dime. They are discrete with no tendency to confluence and are definitely indurated. There is an area of marked erythema of the anal cleft just over the coccyx. On the right side of the anal orifice involving about one-half the circumference is a raised, eroded lesion with a bright red surface and a clear, serous discharge. The margin of the lesion is sharply outlined and the upper border disappears into the rectum. On palpation there is marked induration externally and on digital examination the lesion is found to extend about one-half inch into the rectum, the upper margin being sharply limited and the lesion indurated throughout. The lesion is quite painful to the palpating finger and bleeds but very little. The long bones are free of painful nodes. The spleen is palpable at the costal margin and the liver is felt about two fingerbreadths below the costal margin in the anterior axillary line. The reflexes are present and equal on both sides.

A dark-field examination of the anal lesion revealed large numbers of Spirochete pallida and later the Wassermann report on the blood was returned ++++ positive. During his stay at the hospital a lumbar puncture was done, the fluid withdrawn showing no increase in albumin or globulin, six cells and a negative Wassermann reaction.

A psychiatric examination was made for the purpose of determining any homosexual tendency in the patient, but this revealed only a slightly subnormal mentality without the homosexuality so often found in these cases.

Antisyphilitic treatment was instituted and the patient made a rapid, uneventful recovery.

For the privilege of describing this case my thanks are due Professor Udo J. Wile.

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Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs, Arkansas.

WM. H. DEADERICK, M.D., EDITOR

OCCURRENCE OF SYPHILIS AS EVIDENCED BY ADMISSIONS TO THE CITY HOSPITAL.—James B. Cross, Buffalo, N. Y. New York Medical Journal, 1919, vol. cix, p. 1123.

One of the most interesting and instructive features of this investigation was the study of the lesions encountered and a consideration of their effect upon the community. As a matter of convenience these lesions were divided into the usual three stages: primary, secondary, and tertiary. There were 23 per cent of the patients with primary lesions, which were subdivided into 20 per cent of the genital organs, and 3 per cent extragenital. There were 37 per cent with secondary lesions, 26 per cent of which showed mucous patches, 20 per cent macular and papular eruptions, 3 per cent of these also having palmar syphilides, 1 per cent showed condylomata. There were 39 per cent with tertiary lesions, these being subdivided into 13 per cent ulcers and gummata of skin and cellular tissues; 5 per cent gummata of bone, one-half of these being ulcers through the hard palate: 15 per cent syphilis of the nervous system which included cases of paresis, locomotor ataxia, and various paralyses and patients complaining of indefinite nervous symptoms in whom repeated Wassermann tests were found positive; 3 per cent showed syphilitic manifestations in the eye; 1 per cent of testicle, and 1 per cent of joints and internal organs. Approximately 2 per cent showed hereditary syphilis. The routine method of treatment now in use at the Municipal Hospital is to give nine intravenous injections of arsenobenzol; giving an injection every fourth day. In preparation for treatment, the patients are given a cathartic the day before and no food for at least six hours before and six hours after treatment. Of course, the heart, lungs and urine are subjected to a routine examination before any treatment is given. The gravity method is used in administering the arsenobenzol. If any lessons are to be drawn from this study it seems the following stand out most prominently: 1. The inadequacy of treatment given by the average practitioner both past and present as demonstrated by the large proportion of tertiary lesions, and the treatment of new lesions having been practically limited to local treatment of ulcer. 2. The large proportion, practically sixty per cent who were a positive menace to the community at large, through drinking cups, tableware, coughing and sneezing in public places, holding to street car straps, and other articles of general use. 3. The great value of the Wassermann test as an aid in diagnosis. 4. The necessity for hospitals devoted exclusively to the care and treatment of venereal diseases.

Pathology of Neurosyphilis and Its Relation to Prognosis.—Frank R. Starkey, Detroit, Michigan. The Alienist and Neurologist, 1919, vol. xi, p. 119.

Paresis is characterized in the beginning by a leptomeningitis which is infiltrative or exudative and by perivascular infiltration especially affecting the small vessels and rather diffusely distributed through the cortex, but more intense on the periphery. Tabes is in the beginning a syringoleptomeningitis. Cerebrospinal syphilis is essentially a vascular process; leptomeningitis, which especially affects the nude or unprotected portions of the nerves in the basillar portion of the brain and cord and is accompanied, as a rule, by a gummy exudation, although it may be diffuse and closely resemble paresis, the plasma cell, with its mantle arrangement, being the chief differential element. All of the symptomatology of syphilis of the central nervous system, either paresis, tabes or cerebrospinal syphilis may be present when the disease is still in the leptomeningitis stage, and there is no absolute method of differentiating this exudative, nondestructive, curable stage from the later productive, destructive, incurable stage, the laboratory findings are frequently conflicting and very misleading and it is probable that several of these stages may occur synchronously. The cerebral leptomeningitis may cause any of the signs of paresis, except those of the most advanced stage, and the syringoleptomeningitis may produce all of the symptomatology of tabes and in so far as the condition is exudative, it is curable. In so far as it is productive, we are apt to have very decided remissions, either with or without treatment. In so far as the condition may be destructive, it is necessarily hopeless so far as any restoration of the destroyed tissue is concerned. Following this exudative process we have in paresis increase in glia and all forms of cell destruction, including Nissl's grave cell disease. Finally, as the areas of destruction increase in size and coalesce, a very distinct diffuse destruction of the brain is discernible; and in tabes, following the meningitic exudative stage, we have the parenchymatous degeneration of the posterior columns; and in posterolateral syphilitic disease and diffuse syphilitic myelitis, we have similar parenchymatous destruction. But we must remember these are end stages which may be aptly likened to cavitation in pulmonary tuberculosis. We do not jump immediately from the exudative to the massive destructive stage. This massive condition is only arrived at after destruction cell by cell and fiber by fiber. In most cases of tabes, even though in a very advanced stage some functioning fibers are easily demonstrable. This condition in tabes, however, can not be likened to the picture we see in disseminated sclerosis, wherein numerous axons pass through the sclerosed area intact and the pathways to which they go are not destroyed.

Recurrence of Oral Syphilitic Lesions During Treatment with Mercury.—G. O. Scott, Ottawa, Ont., and G. H. J. Pearson, London, Ont. Journal of the American Medical Association, 1919, vol. lxxii, p. 1064.

Were it not for the demonstration of Spirochete pallida one would be inclined to look on these lesions as the herpetic ulcerations which Hutchinson states are of common occurrence in the mouths of patients suffering from syphilis, but the finding of the organism definitely vouches for their specificity. All three cases are similar in that the patients had received the routine War Office treatment and were all on mercury and potassium iodide when the lesions developed. The lesions did not develop at the site of former lesions, but were of the type that McDonagh designates as autoreinfection. In two of the cases the general health of the patients was poor, but in the third case the general health was apparently good. In one case there was a mild mercurial stomatitis which later developed into a severe Vincent's infection, but all three were receiving careful dental treatment. Akatsu and Noguchi have demonstrated that Spirochete pallida increases its resistance to both arsphenamine and mercury *in vitro.* There is no reason why this can not occur *in vivo,* and in these cases the resistance was increased against the mercury owing to its prolonged use, while the spirochete disappeared and the lesions healed as soon as the patient was placed on arsphenamine. There was no increased resistance against the latter substance, as the patients had all been a considerable time without treatment by it. In these cases it seems very probable that the mercury lowered the tone of the tissues of the mouth; and the Spirochete pallida, being mercury fast, was given a fertile field in which to grow.

Syphilis of the Stomach: A Review, with Notes on a Case of Syphilitic Pyloric Stenosis.—S. W. Sappington, Philadelphia. Hahnemannian Monthly, 1919, vol. liv, p. 357.

Syphilis of the stomach is rare but is not so uncommon as physicians believe. The conception of the gastric lesion as a gross gumma is an erroneous one: the pathology involves a microscopic cellular infiltration, diffuse or focal, which in its ultimate development produces a clinical picture closely resembling other gastric diseases, notably cancer and peptic ulcer. A positive Wassermann reaction, an acidity or achylia, and demonstrable lesions shown by the x-ray are sufficient evidence for entertaining the possibility of luetic infection of the stomach and should lead to the therapeutic test of antisyphilitic drugs. The tentative diagnosis may be confirmed by very remarkable improvement. If our suspicions are incorrect, little will have been lost.

TERTIARY SYPHILIS OF THE NOSE AND THROAT.—Samuel Salinger, Chicago. Illinois Medical Journal, 1919, vol. xxxv, p. 126.

Tertiary lesions of the upper air passages occur not so infrequently but that they should be readily recognized by the general practitioner, who usually is the first to see them. These lesions, when discovered early, are very amenable to treatment, and the results obtained in most cases mean complete restitution of structure and function. When undiscovered and untreated, however, they lead to dire results, such as destruction of important tissues, deformity and loss of function. Tertiary lesions may appear anywhere along the upper respiratory passages from the vestibule of the nose down to the subglottic space in the early form either as a gumma or a chondritis, and later as an ulcer which is either circumscribed, deep and destructive, or else superficial and serpiginous. They are most frequently found on the bony septum of the nose, the hard or soft palate, posterior wall of the pharynx, epiglottis and its folds. The same lesions may be found in the pharynx and palate. The symptoms usually complained of are loss of appetite, earache, sensation of a foreign body in the throat and at times regurgitation of food through the nose. Pain, though frequently severe, is often slight or entirely absent and, therefore, not a symptom of any great value. Gummata of the larynx may be found on the epiglottis and its folds, over the arytenoid cartilages and the ventricular bands. They must be differentiated from a beginning malignancy which in some cases is difficult. The usual symptoms of tertiary lesions of the larynx are dysphagia, husky voice, brassy cough, and profuse expectoration of mucus.

SYPHILIS OF THE STOMACH.—M. Ford Morris, Jr., Atlanta, Ga. New York Medical Journal, 1919, vol. cix, p. 807.

The increase in the number, as well as the proportion, of persons infected with lues will, of course, result in an increase in all the manifold activities of these organisms. Although the pale Spirochete multiplies within the bodies of many million people, and although no organ or tissue within the human body, except possibly the prostate gland, is immune to the causative organism of syphilis, the stomach apparently suffers rather infrequently as the result thereof. The apparent rarity of syphilis of the stomach is due to the fact that this condition is not considered in some of the textbooks of medicine, and also to the fact that it is often overlooked or diagnosed as carcinoma, ulcer, and various other common afflictions. Such mistakes are excusable, because the symptomatology and clinical findings, in this disease, have not yet been put upon a sound diagnostic basis. But the clinical picture of gastric lues is becoming better known. One of the reasons a diagnosis of syphilis of the stomach is not easy is the fact that syphilis manifests itself in a number of lesions. The following types have been described: 1, Gastric ulcer of syphilitic origin; 2, syphilitic tumor of the stomach; 3, syphilitic stenosis of the pylorus; 4, syphilitic cirrhosis of the stomach; 5, chronic gastritis; and 6, perigastritis. It is evident, therefore, that the symptoms resulting from such a multiplicity of lesions will be varied in character and in severity. The symptoms most frequently encountered are pain, emaciation, tenderness; less frequently occur, in addition, hematemesis and melena. In some cases vomiting and pain after eating are the principal symptoms. After studying several cases, and after reviewing much of the literature on this subject, the author comes to the conclusion that syphilis of the stomach has no clear-cut symptomatology and no certain clinical findings; that the diagnosis is best made by the process of exclusion; that the x-rays are of great assistance in arriving at a correct diagnosis. He feels certain that many cases of syphilis of the stomach have been diagnosed as peptic ulcer or gastric carcinoma. And he believes that every case of ulcer of the stomach which does not yield to treatment by the usual dietetic measures should have a course of antisyphilitic treatment before any surgery is done; and, likewise, that every case of suspected gastric carcinoma should be given a short, intensive course of antiluetic treatment, in the hope that such a therapeutic procedure will establish the diagnosis of syphilis, if it is present. The treatment of syphilis of the stomach should be the same as the treatment of syphilis in other organs. In those cases in which pyloric stenosis occurs, gastroenterostomy is usually indicated, in addition to the antiluetic treatment.

SYPHILIS OF THE RECTUM AND ANUS.—Charles J. Drueck, Chicago. Illinois Medical Journal, 1919, vol. xxxv, p. 197.

About the anus may be found the same skin syphilides as occur elsewhere, but all eruptions are modified in appearance by the action of the heat and moisture and the rubbing together of the buttock cheeks. Chancre at the anus occurs frequently enough to be always thought of when an ulcer is seen at or about this opening. Its existence in men is almost proof positive of sodomy, but in women it may occur by accidental contact with the male organ or from vaginal discharges. The chancre may occur on the skin near the anus, between the radial folds, or on the mucous membrane in the anal canal. On the free skin it resembles in appearance a chancre situated elsewhere, but when located between the radial folds or at the anal border it closely resembles an anal fissure. In the secondary stage of syphilis we find two forms of ulcerations: The mucous patch, the ragged ulcer, a sequence of necrosis produced by the strangulation of circulation in the tissue surrounding the syphilides. When the mucous patch appears there also develops the surrounding congestion which interferes with the local circulation, and sometimes the tissue sloughs away. This may happen with any syphilitic eruption about these parts, i.e., papular, macular, pustular, or the small moist papules that appear at the anal folds, on the inner sides of the thigh or about the genitals in any case of syphilis regardless of the location of the chancre. The resulting ulcers are gangrenous, gray in color, irregular in outline, and ooze blood on slight touch. Spirochetes are present in all these lesions which are therefore ready sources of infection.

Syphilitic Induration of the Vulva.—J. F. Gallagher, Nashville, Tennessee. Surgery, Gynecology and Obstetrics, 1919, vol. xxviii, p. 482.

These cases are elephantiasis in gross appearance, they may be called esthiomenes, if that term is to be restricted to the cases in which syphilis is the causative factor, but they are syphilitic in origin, are chronic in their course, and their structure is of an indurative, edematous type. It is possible that what may be the largest percentage of cases that are termed esthiomenes or elephantiasis vulvæ, have been considered of doubtful syphilitic origin because they are highly refractory to antisyphilitic treatment of whatever kind or intensity. Moreover, the microscopic appearance of syphilitic and tuberculous lesions are often confusing. These cases came under observation in the Gynecological Out-Patient Department of Vanderbilt Medical School. Of the latest one thousand patients in that department, only six cases of syphilitic edema of the vulva have been noted. On removal all the tumors showed a marked tendency to bleed, the bases being very vascular. There seemed to be a marked arterial supply and a noticeable absence of veins. The tumor base had an almost characteristic pearly white appearance which exuded a clear serum on pressure. Histologically the specimens showed so striking a similarity in appearance that a description of one will suffice for all. Thickening of the surface epithelium with hypertrophy of the papillae were the noticeable changes in the skin. Underneath these was a noticeable productive inflammation, lymphocytes, plasma cells and eosinophiles being present. Increased fibrous tissues with edema and enlarged lymph spaces are noted which latter are infiltrated with lymphocytes and plasma cells. The blood vessels showed perivascular infiltration. There are giant cells but no caseous masses.

VITILIGO AND SYPHILIS.—John E. Lane, New Haven, Conn. Journal of the American Medical Association, 1919, vol. lxxiii, p. 27.

In the general confusion of dermatologic terminology the achromas and dyschromas are particularly conspicuous, and vitiligo perhaps stands preeminent among them for the vagueness with which the name is used and for the variety of meanings attached to it. There is no general agreement among dermatologists as to what is meant by vitiligo, and almost every one who has written on the subject in English has given it a different signification. A recently observed designation of white scars, such as are produced by gummas or by tubercular syphilides as vitiligo, is an extreme example of what appears to be a misuse of the term. Vitiligo is defined as an acquired dyschroma, characterized by the development of one or more sharply limited spots of depigmentation surrounded by a more or less extensive hyperpigmented border, showing no modification of the structure or function of the skin. It is sharply differentiated from leucoderma, which is an acquired achroma only (that is, achroma without any attendant hyperchroma), and it does not include the rare leucomelanoderma of Fournier or the areolar pigmentary syphilide of the neck, described by Hardy in 1853, and later so thoroughly studied by Fournier and others. Up to the present no other disease has been demonstrated to be present in anything like this proportion in patients with vitiligo, and one deduction at least is certain, that the search for syphilis is demanded in every case of vitiligo.

THE MANIFESTATIONS OF SYPHILIS IN PREGNANCY AND THE NEWBORN.—W. W. Wells, Oklahoma City, Oklahoma. Journal of the Oklahoma State Medical Association, 1919, vol. xii, p. 93.

Syphilis in the female does not show the marked manifestations of the nervous system, as paresis and tabes dorsalis, as it does in the male. In the female, syphilitic ulceration of the cervix may be mistaken for cancer, as the most prominent symptom of both is hemorrhage. Latent syphilis prevails more in the female than in the male. If the primary lesion, located on the cervix, heals, it leaves a dense scar which causes cicatricial stenoses of the os and will dilate, at the time of labor, very slowly. The secondary stage comes sooner and with more virulence, often forming maculopapular syphilides; these may become pustular. The tertiary symptoms come on early and are more extensive, in the form of simple condyloma and gumma. When a syphilitic woman becomes pregnant or a woman is infected with syphilis at the time of conception, interruption of pregnancy is the rule. A syphilitic woman may bear a living child that does not show symptoms of syphilis; but not the first pregnancy after infection; they usually have two or three abortions progressing further along in pregnancy each time, then one or two still-births, then a living child which dies soon after birth; and finally a living child which may show no symptoms of syphilis.

SYPHILIS OF THE LUNGS.—M. Ford Morris, Jr., Atlanta, Ga. Medical Record, 1919, vol. xcv, p. 722.

In acquired syphilis, the chief pulmonary lesions are (1) gummata, (2) bronchopneumonia, (3) fibroid induration or chronic interstitial pneumonia, and (4) a progressive destructive disease—the so-called "syphilitic phthisis." The symptoms of syphilis of the lungs are not characteristic or distinctive. Coughing is probably the most common symptom—which results from irritation of the respiratory tubes or from changes within the lungs. The coughing usually produces offensive, yellowish or greenish-colored sputum. Hemoptysis also is a common symptom. Sometimes the blood is just sufficient in amount to tinge the sputum, but at other times it is more profuse. Loss of weight and strength occurs in practically all of the cases. Night-sweats are not infrequent. Dyspnea occurs in some of the cases. Fever is present in many of the cases; often this pyrexia is of the tubercular type. The physical signs, like the symptoms, are neither characteristic nor distinctive. The physical findings are, of course, dependent upon the character of the lung lesion. The diagnosis of pulmonary syphilis is made by exclusion. Tuberculosis must be ruled out. In order to rule out tuberculosis as the cause of such symptoms as were mentioned, one must resort to every valuable test—especially the staining of sputum which has been digested by sodium hypochlorite, the inoculation of guinea pigs, and the complement-fixation test for tuberculosis. One should not give potassium iodide as a therapeutic test until all other tests have been given negative results. Patients who have syphilis of the lungs may give a syphilitic history; they usually have evidences of syphilis elsewhere than in the lungs; and they practically always have a strongly positive Wassermann.

SYPHILIS OF THE TESTICLE.—S. William Schapira, New York. Urologic and Cutaneous Review, 1919, vol. xxiii, p. 321.

The author's experience among the civilian population in New York showed us that clinically recognizable involvement of the other genital organs in the syphilitic process—together with that of the testicle—is rare indeed. Among the troops treated in the genitourinary department of a base hospital where almost all the men were from southern states, they found a different picture. Nine cases of clinically recognizable syphilitic testicle were seen. The diagnosis was confirmed by the history, by serologic tests and by the results of treatment. Of the nine cases, six were clinically unilateral and three bilateral; the epididymis, the lobe of the prostate and the seminal vesicle were involved with the orchid of the same side; in the bilateral cases these parts were bilaterally involved. All these cases responded well to routine antisyphilitic treatment, intravenous injections of arsphenamine and intramuscular injections of mercury. In two patients the hydrocele fluid was present in such amounts that the testicles could not be palpated. After evacuation of the fluid in open operation the testicles were found to be enlarged and hard. One of these hydroceles was shaped like a miniature Zeppelin, eight inches long.

A CASE OF MULTIPLE CHANCRES OF THE PENIS.—James C. Sargent, Milwaukee. Journal of the American Medical Assn., 1919, vol. lxxii, p. 100.

That both lesions represent the same infection, one developing after four weeks' incubation and the other after eight weeks' incubation, seems altogether improbable. There remain but two other possibilities: the first, that the right chancre represents the original infection contracted four weeks before its appearance, and that after a second incubation period of four weeks, a transplanted chancre developed on the left; the second, which seems the more probable, that the right chancre was contracted August 10 and the left chancre September 3, each developing after four weeks' incubation.

THE SYPHILITIC FACTOR IN INSANITY.—W. A. T. Lind, Victoria, Australia. Medical Journal of Australia, 1919, vol. i, p. 187.

It would be absurd to claim that syphilis is the cause of every insanity, but it is not far short of the truth to say that the combination of psychopathic inheritance, and acquired or congenital syphilis, is costing the public purse of Victoria a good round sum every year. The age of the general paralytic (acquired) used to be somewhere about 49, but, judging by the postmortem examinations of the last few years, it seems to be gradually approaching 30. In other words, syphilis is acquired almost before the youth is mature. It looks as though the stone, bronze, and iron ages will be recognized by posterity as being followed by the syphilitic age. A number of the victims of venereal disease know something in a vague manner of the risks run through illicit intercourse, but many of them have no idea that serious consequences (to themselves) could follow such acts. For the sake of the ignorant, the author would suggest the use of the same wall sheet warnings concerning venereal disease as were issued in the case of meningitis and smallpox. We see on every pier and shore instructions for resuscitating the apparently drowned, why not a law that every factory, bank, shop, etc., where there are wage-earners should have a wall sheet on the dangers and consequences of venereal disease, drawn up by the health department. It is not sufficient in contemplating these evidences of sexual precocity to shrug our shoulders and say with Max Nordau "fin de siecle." Those of us who see most of the seamy side of humanity should make known any facts which intimately concern the welfare of the race.

DIASTATIC ACTIVITY OF THE BLOOD IN CANCER, SYPHILIS AND DIABETES. —H. H. DeNiord and B. F. Schreiner, Buffalo. Archives of Internal Medicine, 1919, vol. xxiii, p. 484.

There is a low diastatic activity in diabetes associated with syphilis. The internal secretion of the pancreas is probably inhibitory to the activity of the disease in the blood. Exposure to roentgen rays for either long or short periods of time does not alter the activity of the diastase, but in some cases temporarily lowers the sugar content of the blood. There is nothing especially characteristic of either the blood sugar or diastase of the cancer patient at any stage of his disease. Miscellaneous nondiabetic cases show normal sugar in the blood with normal or low diastatic activity; or high sugar with increased or low diastatic activity; but never low sugar with high diastatic activity. The diastatic activity tends to increase with rising sugar in the blood, especially with a dietary glycemia. In dietary correction of a hyperglycemia the diastatic activity decreases with the sugar, whether in a diabetic or not.

AN ANOMALOUS FORM OF PAPULOPUSTULAR SYPHILIDE.—Civatte. Annales de Dermatologie et de Syphiligraphie, 1919, vol. vii, p. 123.

The author has seen but four of the cases under consideration, all in African Mohammedan troops. The phenomenon is something more than a coincidence. The first case was in a Moroccan of about twenty years of age and cachectic look. An eruption of a most disseminate character had begun several weeks before. Most of the surface was involved, only hands and feet being exempt. There was a certain symmetry and a marked polymorphism, and the lesions were thickly present. Study showed that the plaques which constituted the lesions were made up of closely confluent papules, each surmounted by a scale or minute crust. These elemental lesions were from 2 to 3 mm. in width. The plaques thus formed were of variable size and in some localities—for example the buttocks—were as large as the palm of the hand. The entire picture was apparently due to the varying degree of coalescence of these minute lichenoid papules which in some localities were isolated, in others aggregated to form small plaques of 2-3 cm. across and in still others, as already mentioned, as large as the palm of the hand. In the majority of these primitive papules a hair was present. In other words the lesions were of the type of a lichen. The chief difference was the tendency to form a drop of pus which also dried to form a crust, whence the designation papulopustulous. The minute size of these lesions leads the author to speak of them as "papulopustulettes." In one case the designation "acneiform" was applicable, although not found in the acne area. A location of especial interest in these cases was the external genitals and apparently the lesions attained their fullest flower in this region.

Glans, furrow, pubes, all showed their presence. An observation of this kind must necessarily be incomplete and further research will be necessary to give the lesions autonomy. The author has found nothing of the type in literature.

FORMS AND TREATMENT OF BRONCHOPULMONARY SYPHILIS.—Plique. Journal de Médecine et de Chirurgie Pratiques, 1918, vol. lxxxix, p. 321.

In congenital syphilis the lungs are affected with nearly the frequency of the bones. Functional disturbances comprise dyspnea, paroxysms of coughing, hemoptysis—which is very rare—and intermittent fever which is quite common. Defervescence occurs during the night and is accompanied by profuse perspiration. The patient's tolerance is remarkable especially in tertiary syphilitic fever. In children with congenital syphilis tracheobronchial adenopathy is generally of specific origin. The disease usually appears in the lungs about the fifth year, this constituting a late stage, but numerous cases are on record in which lesions have appeared in the early years and even early months of life. On the other hand, the late form may not appear until adolescence. The lesions to which the author refers are gummatous, in part, but the usual chronic affections of the chest may also be closely simulated as cavitary tuberculosis, sclerosis of the lung and bronchiectasis while a diffuse chronic pneumonia is also described.

In chronic pulmonary affections the absence of tubercle bacilli in the sputum, a positive seroreaction and the coexistent clinical evidences or history of syphilis are valuable aids to diagnosis. It must not be overlooked, however, that tuberculosis may attack a syphilitic lung. In these chronic syphilitic pneumopathies the course is long, lasting perhaps for years when untreated. Specific medication often works wonders in these cases, but it must be remembered that spontaneous cure is not unknown.

ANEURYSM AND AORTIC INSUFFICIENCY OF TRAUMATIC ORIGIN IN A SYPHILITIC.—Ramond and Postina. Bulletin Médical, 1918, vol. xxxii, p. 170.

The authors' observation concerned a soldier of twenty-eight years who was thrown violently to the ground face downward through the explosion of an air torpedo at a distance of 30 meters. When examined a month later he presented increased cardiac dullness, a retrosternal systolic thrill and a well-marked scraping aortic sound on diastole. Radioscopy showed aortic bulging in the middle portion of the right border of the aortic arch. The patient died with aortic symptoms about 5 months after his injury. Autopsy revealed existence of three aneurysmal dilatations of the aortic arch, an aortic insufficiency which was functional but not mechanical (water poured into the aorta penetrated freely into the left ventricle), and arteritic patches of a clearly syphilitic character under the microscope. Although the patient gave no history or evidences of syphilis prior to his admission, a very decidedly positive Bordet-Wassermann reaction had been shown. The aneurysm may therefore be regarded as of syphilitic origin while the trauma was merely an accidental determining factor, which in the first place affected the anterior thoracic wall when the patient was flung face downwards. The enormous liberation of gas in the air torpedo with its great destructive effects must also be taken into consideration. Compressed gas exerts a relatively slight action on the lungs for the closure of the glottis follows at once on the increase of external pressure. The patient did not suffer any pulmonary damage but the mechanical compression exerted by the gas on the surface caused marked vasoconstriction and the fright acted synergistically so that a notable rush of blood ensued to the large vessels and heart with overburdening of the aorta and ventricles, both of which being already diseased underwent dilatation and its sequelæ.

THE PATHOLOGY AND THE CYSTOSCOPIC DIAGNOSIS OF THE TABETIC BLADDER.—R. N. Duffy, New Bern, N. C. Mississippi Valley Medical Journal, 1919, vol. xxvi, p. 113.

It is possible for the cystoscopist to be the first to diagnose a beginning tabes in certain instances where the bladder symptoms constitute the predominant feature. In patients complaining of frequent urination, especially if this is accompanied by dysuria, and in whom examination of the urine, the urethra and adnexa and the bladder is negative, tabes should be thought of and the patient tested for absence of knee jerk, the presence of Argyll-Robertson pupil, and the Wassermann reaction in the blood and spinal fluid. In patients complaining of difficulty in urinating in whom no obstruction is found to the outflow of urine and the cystoscope shows a trabeculated bladder, a nerve lesion is the cause of the trouble and the most probable diagnosis is tabes. Subsequent test should confirm this. In patients suffering from an overflow incontinence in tabes, the diagnosis is only too evident and requires no special consideration.

STUDIES ON A FORM OF PULMONARY SYPHILIS NOT HITHERTO RECOGNIZED.—Leredde, Paris. Annales des Maladies Vénériennes, 1918, vol. xiii, p. 760.

The author has studied 20 cases of acute bronchitis with pulmonary congestion, some of which presented emphysema and asthma. The patients were all syphilitic, the disease being apparently congenital. The author summarizes as follows: congenital syphilis may give rise to a syndrome characterized by dyspnea on exertion, recurrent bronchitis, emphysema and at times asthma. A positive seroreaction was present in some of the patients while others showed stigmata which were doubtless of syphilitic origin. The process in the lungs is probably one of sclerosis of an active character. It also serves as a predisposition for other pneumopathies, such as infections—bronchitis, pneumonia and pulmonary tuberculosis, especially the latter.

When confronted with this affection one should seek to prove or exclude the presence of syphilis in all recognized ways, not forgetting an examination of the cerebrospinal fluid. In the clinically tuberculous this point should be made. Likewise in attacks of recurrent bronchitis, in emphysema and in any other affection of the chest with exertion dyspnea in which the rationale is obscure. The presence as a factor of syphilis is of more than academic interest, for systematic and persistent treatment with the most active specific medication may give rise to results not anticipated from the clinical picture.

THE OCCURRENCE OF UNSUSPECTED INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM IN UNSELECTED CASES OF SYPHILIS.—Paul Fildes, Roderick J. G. Parnell, and H. B. Maitland, Haslar, England. Brain, 1918, vol. xli, p. 255.

The authors have examined 624 syphilitic men, of whom the great majority were in the early stages of the disease and showed no obvious signs of nervous disease. Of these, 18 per cent showed undoubted signs of an abnormal condition of the central nervous system. Thus they are able to confirm the work of earlier writers, although the number of abnormal cases is considerably less in their series than in those of some others. This is partly due to the fact that cases they have described as "doubtful" are not included in this estimate. If, as they consider justifiably, these also are looked upon as abnormal, the percentage of affected men reaches 30. Even this figure is not so high as some found in the literature, and it should be understood at once that statements of the numbers of men affected are totally devoid of significance, unless accompanied by an indication of the stage of the disease. They have found that there is a pronounced difference in the incidence of abnormal conditions at different stages of infection. There is a progressive increase of these up to the secondary stage, but a slight decline in the later manifest secondary and tertiary period. In the case of those men, however, who show no symptoms (namely, the so-called latent stage) there is a pronounced increase in the number affected. In their series, of all men who have been affected for more than six months and showed no symptoms, no less than 35 per cent had abnormal central nervous systems. If the number of men found to be abnormal by us is less than appears from the work of some other authors, this is adequately explained by the fact that this series includes a large number of men in the first weeks of the disease. The onset of the abnormality may be very early. It was even demonstrable in two cases before the Wassermann reaction had become positive in the serum after infection. The nature of this abnormality in the central nervous system does not admit of doubt. It is a syphilitic meningitis. The authors found this opinion not only upon the presence of lymphocytes in the cerebrospinal fluid, but also upon the frequent appearance of polymorphonuclear leucocytes in the more pronounced cases. Furthermore, in a large proportion of the abnormal cases, the fluid showed a positive Wassermann reaction, while in one case they even found S. pallida by the method of dark-ground illumination. There is no evidence that previous arsenical treatment increases either the number or severity of the affected cases. An outstanding feature of these cases is the almost total lack of symptoms. Very few of the men complained of any disability even when the meningitis was acute enough to produce a visible opalescence in the cerebrospinal fluid. Very few of these men showed any clinical signs of nervous disease detectable by examination. On the other hand a considerable proportion of the abnormal cases had lesions of the eye grounds, which were indeed of slight extent, but which, nevertheless, indicated a commencing retinitis. A certain number of cases showed affections of the internal ears, but there was no evidence that these were commoner than among nonsyphilitics or syphilitics with apparently intact nervous systems. Antisyphilitic treatment has a marked ameliorating action upon these conditions. Some are rapidly reduced to normal, while the great majority were shown to be improved within the period of observation. On the other hand, a few of the cases showed a remarkable resistance to treatment, indeed the meningitis actually progresseed in spite of repeatedly renewed treatment. Although the demonstration of a negative Wassermann reaction in the serum denotes that an affection of the central nervous system is improbable, nevertheless it does not exclude it, and in view of the importance of early treatment (and the value of the operation in prognosis) it is probable that lumbar puncture should never be omitted as a routine in the examination of all cases of syphilis.

FIVE CASES OF NEUROSYPHILIS ILLUSTRATING SPECIAL POINTS IN SYMPTOMATOLOGY AND COURSE.—Abraham Myerson, Boston. Boston Medical and Surgical Journal, 1919, vol. clxxx, p. 499.

These cases are reported because they represent somewhat unusual and yet rather important phases of neurosyphilis. The first case deserves attention because it points out the importance of the spinal puncture. It is very well known that the spinal fluid may be positive to the Wassermann test for syphilis where the blood is negative. But in this particular case, the blood remained negative during many examinations while the spinal fluid was constantly positive. The second case is noteworthy because the Brown-Sequard syndrome appeared in almost classic purity. Moreover, the spinal fluid showed the xanthochromia syndrome. The third case is one in which a mental disease apart from the neurosyphilis manifested itself almost as though the neurosyphilis were not present while the neurosyphilis itself gave practically no symptoms. The fourth and fifth cases are important because they affect a brother and a sister. The brother, a paretic, clinically, was treated and had a fine remission of clinical symptoms, but the spinal fluid was unchanged. The sister, presenting none of the signs of paresis, was treated for a long time for orthopedic symptoms. She presented in her spinal fluid the syndrome of paresis. Altogether, these cases form a group which, though each is individual and unusual, is characteristic of neurosyphilis in the wide range of symptoms presented.

A Case of Diabetes Mellitus With Syphilis.—J. W. Mitchell, Lakewood, N. J., American Journal of the Medical Sciences, 1919, vol. clvii, p. 700.

Though probably diabetes is relatively infrequently due to syphilis, search for this cause, whether inherited or acquired, should be carefully made by all possible means, and merely a negative Wassermann reaction in the blood should not be accepted as excluding it; diabetes, particularly in the advanced stage, may not be (and probably as a rule is not) perceptibly altered by antiluetic treatment. This is logical from the fact that syphilis here presumably produced fibrous changes in the pancreas just as it did in the liver. What can be hoped from such therapy is the checking of further advance of the infectious process, not the repair of existing damage and the improvement of the diabetes. Such cases stand practically on the same plane as diabetes from other causes, and the same dietary control is necessary. It will be noted that the diabetes in this case is of marked severity, as shown by the minimal tolerance acquired in long treatment. The patient has been benefited in respect to strength, comfort, and presumably longevity, but the ultimate outcome in view of the advanced conditions present is dubious.

General Paralysis and the War.—Kahn. Journal de Médecine et de Chirurgie Pratiques, 1919, vol. xc, p. 197.

The author concludes that the war has been without influence on the frequency of this affection but that the interval of latency may have been shortened, while in some cases the course is accelerated. Points which may be determined in a few years relate to the percenttage of cases of paresis in cases of syphilis which have developed during the war. Other subjects of interest are presence or absence of a special strain of spirochete, early meningitis and its influence on the development of paresis, possibility that the meningocortical region is an area of least resistance. The meningoencephalitis of syphilis has no relation to any other state which induces dementia, and produces so-called general paralysis. The criteria here include bacteriology, the clinic and biological resources. Traumatisms, exhaustion, and emotional states are not necessary for the production of this affection.

CONGENITAL PULMONARY SYPHILIS.—Canelli, Turin. La Pediatria, 1919, vol. xxvii, p. 11.

Infantile pulmonary syphilis is chiefly congenital and is both frequent and deadly with diagnosis frequently anatomic. In the congenital case infection occurs frequently via the portal route. The principal lesions are the gumma, bronchiectasis, and pneumonia. Bronchiectasis may in some cases be primary. One may speak in these infantile cases of ulcerated syphilomata of the lung. The types of pneumonia encountered comprise interstitial, epithelial or desquamative, fibrosclerotic and adenomatous, with mixed forms. White pneumonia corresponds to the epithelial form. The pleura is usually involved in lung syphilis. Tuberculosis of the lung may be seen associated with these syphilitic pneumonias. Histologically the lesions are seen to be very complex. The spirochete is often seen in white pneumonia.

INFANTILE SCURVY ASSOCIATED WITH HEREDITARY SYPHILIS.—Roy M. Greenthal, Ann Arbor, Mich. American Journal of Diseases of Children, 1919, vol. xvii, p. 440.

The roentgenograms of the bones of the lower extremities reveal three interesting findings: (1) a "white line" at the epiphyseal margins; (2) multiple fractures of both femurs and tibia situated just above the epiphyses; (3) periosteal thickening of the shafts of the bones, especially of the femurs. Several possibilities are to be considered in the diagnosis, namely, syphilis, rickets, osteogenesis imperfecta, scurvy. The family history, physical findings—snuffles, palpable liver and spleen, adenitis, positive Wassermann reaction on both child and parents—prove conclusively that syphilis is present. A "white line" at the epiphysis may suggest rickets. This line is not the smooth, broad line seen in scurvy, but a jagged, irregular line. The epiphysis appeared frayed out. The "white line" does not occur until after the process has healed, and other characteristic bone changes, which are not present in this case, are usually seen. Osteogenesis imperfecta is suggested because of the multiple fractures. There are no other signs of this rare disease present, however, such as the thinning of the cortex and diminution of calcium in the medulla of the bone. Scurvy will explain all of the bone changes.

The smooth "white line" at the epiphysis is regarded by all authorities as diagnostic of scurvy. The "white line" does not occur in hereditary syphilis. Multiple fractures are not a common complication of scurvy, but they do occur. In scurvy the bones are somewhat more fragile than normal, and fractures might easily occur. The periostitis, characteristic of scurvy, is a localized one, and is not of the girdle type. This is the condition found in this case. It would seem that both syphilis and scurvy are present in this case: syphilis on the grounds of the history, physical findings, and Wassermann reactions; scurvy on the grounds of characteristic bone pathology, changes in the gums and striking response to the administration of orange juice.

THE VENEREAL SORE PERIL.—A. Strachstein, New York. Medical Record, 1919, vol. xcv, p. 775.

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What are the important data to investigate when confronted with the diagnosis of a genital ulcer? The following points enumerated, if carefully and jointly utilized in the diagnosis, would practically eradicate all sources of error: 1. Any genital sore appearing over ten days after exposure is most likely a chancre. This, however, is not reliable if the agencies of infection were more than one during that stipulated time. 2. Chancres may be single or multiple, contrary to many textbook writers, who cling to the old version that a single one is a chancre, and when multiple they are chancroids. In the writer's experience, the appearance of the ulcer is very helpful. The chancre is usually a clear-cut, punched-out ulcer having a clean, healthy, and beefy-looking floor. Induration, when present, is diagnostic, but the chancre may be very superficially situated without any induration whatever. There is a sharp line of demarcation of the edge of the ulcer and the tissues surrounding it show no inflammatory changes. The edge is neither elevated nor serpiginous in contour. These features, of course, may vary when there is a secondary infection. There are a great many instances in which the clinical features are so pronounced that one is justified in making a diagnosis of syphilis rather than call the lesion a simple ulcer because two or three examinations have failed to reveal the presence of Spirochete pallida. 3. A positive finding of the Spirochete pallida in an ulcer makes the diagnosis conclusive; but negative findings, no matter how many times done, do not by any means exclude syphilis. 4. The Wassermann test. This serologic test is of particular value in those cases in which the observer has no opportunity to study the lesion in its earlier days; also when in repeated examinations by the darkfield vision spirochetes can not be found. One must, however, bear in mind that this reaction does not appear early. Hence, a negative darkfield examination and an immediate negative Wassermann by no means exclude syphilis. In order to exploit the full value of this test the blood should be examined during the sixth, tenth, and fourteenth weeks after exposure to the infection before we can say positively that the patient has a negative Wassermann. These conclusions are based on actual experiences with this test.

SYPHILIS AT THE U. S. ARMY BASE HOSPITAL, CAMP GREENE, CHARLOTTE, N. C.—Clyde F. Ross, Richmond, Va. Virginia Medical Monthly, 1919, vol. xlvi, p. 57.

No one sign, either laboratory or clinical, should be depended upon for the diagnosis of syphilis, but the laboratory and clinical signs should be closely examined and conclusions reached by a study of all the information available, never forgetting that the diagnosis of syphilis was made long before the advent of the Wassermann. The ideal time to begin treatment in syphilis is before the appearance of the positive Wassermann during the primary stage. This should be our aim in our future relations to the treatment of this disease. Nine per cent of the author's cases of chancre were multiple, while 13 per cent were of the mixed variety; that is, both chancres and chancroids were present. Primary syphilis can be diagnosed and all active lesions healed in twenty days, with an average administration of three doses of arsphenamine and two injections of mercury. Secondary syphilis can be diagnosed and all active lesions healed in sixteen days and with two and a half doses of arsphenamine and two injections of mercury. The administration of arsphenamine is not without danger and it should not be administered except when indicated, which indication is the existence of syphilis, active or latent, and then only under the best conditions possible, and by one who can meet any emergency that may arise. The negro is more amenable to treatment than the white man, as shown by the length of time spent in the hospital by the two classes of patients.

DIAGNOSIS OF SYPHILIS OF BONES AND JOINTS.—James O. Wallace, Pittsburgh, Pa. Journal of Orthopædic Surgery, 1919, vol. i, p. 258.

That syphilis of bones and joints has been largely overlooked in the past is evident from the relatively small number of cases in our hospital records and in the literature. This is naturally more noticeable in the period before the x-ray and Wassermann were in general use. At the present time we exclude syphilis either as a primary or complicating factor, in all cases of bone and joint disease. Syphilis is often present as a complicating factor, or may be merely coincidental, in cases where the bone or joint disease under consideration has some other etiologic factor as tuberculosis, osteomyelitis, or rachitis, so that a history of syphilis, the presence of other manifestations of the disease, or a positive Wassermann does not prove that the bone or joint disease under consideration is syphilitic. In one of the author's cases, a positive history of syphilis was present and a positive Wassermann, but the patient did not improve under antisyphilitic treatment, but became progressively worse, and the bone disease later proved to be tuberculous. A tuberculous spine did not improve under treatment, and syphilis was later demonstrated as a complicating factor. One must not forget that a positive Wassermann on one hand or a positive von Pirquet on the other is not *prima facie* evidence that the disease alone exists: that syphilis is an excellent medium for the implantation of tuberculous infection, or any other infection. A history of syphilis or the presence of other manifestations of the disease is of value in suggesting the presence of syphilis, but not of any diagnostic value, as it does not exclude the presence of tuberculosis or other bone and joint diseases. In studying symptoms and physical signs alone the author has been unable to differentiate syphilis of joints from that due to other etiologic factors. The author considers the Wassermann reaction very valuable, but only as one point in the diagnosis. In many of his cases the Wassermann reaction was negative, and they were undoubtedly syphilitic, as shown by the x-ray and their response to antisyphilitic treatment. He has also cases in which the Wassermann was positive and in which the cases proved to be some other bone or joint disease. In some of these cases syphilis was undoubtedly a complicating factor because improvement was not marked until antisyphilitic treatment was instituted. A routine Wassermann is taken on all his cases of bone and joint disease, and in those which are negative but in which the clinical symptoms or roentgenograms suggest syphilis, a provocative Wassermann has been found in some cases. He has found the luetin test of value also, as it is sometimes positive when the Wassermann reaction is negative. The finding of a negative von Pirquet in doubtful cases is of value. The author considers the roentgenogram the most valuable factor in the diagnosis of syphilis of bones and joints and in differentiating it from other conditions. In one of his cases there was a history of a primary infection and the Wassermann was positive, but the roentgenogram showed nothing suggestive of syphilis but was suggestive of tuberculosis. In his cases he has not found syphilitic arthritis without bone involvement, as the roentgenogram of the joint involved may show nothing, while a roentgenogram of other bones or those contiguous to the joint may show a typical syphilitic osteoperiostitis. In one of his cases where the knee was complained of, a roentgenogram showed typical syphilitic involvement of the radius and ulna. In studying the roentgenogram of cases he has been unable to discern any difference between acquired and congenital cases, with the possible exception of congenital syphilitic osteochondritis. The so-called therapeutic test is also of some value in the diagnosis of obscure bone and joint lesions where an absolute diagnosis can not be made from the clinical and laboratory findings. In 38 cases of bone and joint syphilis, 22 cases were congenital and 16 were acquired. In 34 cases having x-ray examinations, only 8 cases had an involvement of joint as well as bone.

THE PHENOMENON OF VERNES AND ITS APPLICATION TO THE DIAGNOSIS AND TREATMENT OF SYPHILIS.—Uffoltz. Archives de Médecine et de Pharmacie Militaires, 1918, December (Reprint).

In 1913 Vernes published a monograph on the humoral signs of syphilis in which he figured a graphic based on colorimetry. The curve in question shows an ascending phase of infection and a descending phase which indicates the action of treatment. To build up this doctrine over 150,000 serologic determinations were made. Vernes styles his method syphilimetry and seromensuration, and terms it a transformation of the old Wassermann method. The conflicting results of the Wassermann at the hands of different laboratory men first influenced Vernes to develop a more certain resource. The hemoglobin produced by hemolysis still serves as the coloring principle in diagnosis. In the Vernes method weekly tests are made and recorded, using the same serum throughout, and curves plotted. It was learned that the confirmed syphilitic presented a peculiar oscillating curve, while in the normal subject instead of a curve a straight line is produced. For the refinements of technic the reader must consult the original papers of Vernes before the Academy of Science. The serum of the untreated shows a characteristic instability, while under the influence of arsenic this is favorably modified but recurs when treatment has been insufficient. When a certain amount of treatment has been carried out so that there is no return of the syphilis curve after 8 months experience teaches that the patient is cured. The chief value of the method is the exposure of the latent syphilitic with reference to possible marriage, the suppression of syphilitic infantile polymortality and similar prophylactic uses.

FURTHER OBSERVATIONS ON THE INFLUENCE OF INCUBATION ON THE WASSERMANN REACTION.—E. H. Ruediger, Bismarck, N. D. Journal of Infectious Diseases, 1919, vol. xxiv, p. 405.

Incubation at 1° C. gave stronger positive results that did incubation at 2° C., 3° C., 4° C., 5° C., 6° C., 7° C., 8° C., 9° C., 10° C., or 37° C., while the results obtained at 0.5° C. were identical with those obtained at 1° C. Incubation for 24 hours at 1° C. gave stronger positive results than incubation at 1° C. for 15 hours; incubation for 15 hours at 1° C. gave stronger positive results than did incubation for 10 hours at 1° C.; incubation for 10 hours at 1° C. gave stronger positive results than did incubation for 5 hours at 1° C., and incubation for 5 hours at 1° C. gave stronger positive results than did incubation for 1 hour at 1° C. Incubation for 10 hours at 1° C. gave uniformly good results, while with one lot of complement 15-hour incubation at 1° C. and 24-hour incubation at 1° C. gave bad results. At the present time 10-hour incubation at 1° C. is the longest incubation time which has met all requirements. Twenty-four serums from healthy persons gave negative results under 10-hour incubation at 1° C. and under 15-hour incubation at 1° C. Alcoholic extract of beef heart gave much stronger positive results than did acetone-insoluble antigen of beef heart. The alcoholic extract gave strong positive results at 1° C., while the acetone-insoluble antigen gave stronger positive results at 37° C than at 1° C. At 1° C. alcoholic extract of beef heart gave results that were identical with the results given by alcoholic extract of human heart at 1° C. Acetone-insoluble antigen of beef heart gave much weaker positive results than did alcoholic extract of human heart. Warming the serum-complement-antigen mixture before the sensitized blood corpuscles were added gave the same results as when the sensitized blood corpuscles were added to the cold serum-complement-antigen mixture. Warming the serum-complement-antigen mixture before the sensitized blood corpuscles are added is a decided advantage because hemolysis is much more rapid and agglutination of the corpuscles is much less.

SUPERIORITY OF THE METHOD OF ICE-BOX FIXATION IN THE WASSERMANN TEST.—Oscar Berghausen, Cincinnati. Journal of the American Medical Association, 1919, vol. lxxii, p. 996.

Ice-box fixation, from eighteen to twenty hours at 0° and 2° C., increases the number of positive reactions with serum of known syphilitic patients. There is no evidence to show that it tends to cause false positive reactions. In the examination of a large number of serums, ice-box fixation, simple alcoholic extract of a syphilitic organ being used as antigen, yields satisfactory results.

OBSERVATIONS ON THE WASSERMANN REACTION.—Paul A. Lewis and H. S. Newcomer, Philadelphia. Journal of Experimental Medicine, 1919, vol. xxix, p. 351.

The Wassermann reaction carried out according to the method of McIntosh and Fildes, with cholesterolized antigen and with certain allowances for the presence of native antisheep amboceptor, leads to about the same result as when it is done according to the recent proposal of Noguchi, with the native human complement and acetone-insoluble lipoids as antigen. The differences are such as to suggest that from the point of view of diagnosis the Noguchi method is the more conservative but that there is definite advantage in using two methods as distinct in origin of materials as these, partly for the purpose of control and partly in the hope of acquiring new information of importance. As a measure of control of treatment the cholesterol antigen appears to the authors to be the more valuable. The Wassermann reaction alone, by whatever method it may be done, can only be used in the diagnosis of syphilis in conjunction with presumption based on other grounds. That it fails to appear in a considerable percentage of syphilitics is well known. That the reaction is positive in other conditions is not so generally recognized. Fresh instances of this in certain febrile cases are here recorded.

CLINICAL INTERPRETATION OF THE WASSERMANN REACTION.—Ferrand. Journal de Médecine et de Chirurgie Pratiques, 1919, vol. xc, p. 172.

This article is for the most part a mere summary of our knowledge of serodiagnosis of syphilis. Of special interest, however, is the comparison of the Wassermann and Hecht reactions which not only do not always run parallel but are often frankly dissociated. The Hecht is the more sensitive of the two and naturally gives a higher percentage of positives in the same series. In the chancre period a Hecht positive antedates a Wassermann positive by several days while in late accidents it reappears before the Wassermann. It tends to disappear less rapidly after intensive treatment. Flat dissociation with Wassermann negative and Hecht positive may be encountered in certain types of syphilis, as for example in lues of the eye. The Hecht, or as some term it, Hecht-Weinberg, reaction is now used in most laboratories to check up the classical Wassermann, being regarded as the best of the modifications of the latter in which unwarmed serum is used.

TECHNIC FOR THE WASSERMANN REACTION.—John H. Larkin, Leon H. Cornwall, and I. J. Levy, New York. Journal of Laboratory and Clinical Medicine, 1919, vol. iv, p. 571.

The following technic is employed at the City Hospital Pathological Laboratories in performing the Wassermann reactions. It is, in its essential details, the Wassermann-Citron technic, with certain modifications in accordance with the more recent research advances in this field. The total volume of the reactions is 2.5 c.c., being one-half the amount of the original volume used byWassermann and his co-workers. Each ingredient is diluted, in accordance with preliminary titrations, so that for the test .5 c.c. of each ingredient is added. Blood sera are sent to the laboratory on the afternoon of the day previous to that on which tests are performed. They are allowed to coagulate and stand at room temperature from one-half to two hours. The clots are then carefully separated from the sides of the tubes with a fine sterile wire and the tubes placed in the ice chest overnight. On the following morning the sera are poured off or pipetted from the clots, centrifugalization being resorted to only in cases where the sera are not clear and free from cells. All sera are inactivated in a water-bath at 55° C. for one-half hour. The hemolytic system consists of sheep cells and antisheep hemolytic amboceptor derived from rabbits. Corpuscles are obtained fresh from an abattoir on the day previous to that on which the tests are performed. The whole blood is collected in a sterile glass bottle, tightly stoppered and containing glass beads. It is defibrinated by gentle shaking for fifteen to thirty minutes. After defibrination it is filtered through twelve thicknesses of sterile gauze to remove any small clots of fibrin including, in their meshes, cells. The filtrate is placed in 15 c.c. centrifuge tubes and centrifuged four times at high speed. The first centrifugalization is for 25-30 minutes. The pure serum is then pipetted off and the cells well mixed with .9 per cent sterile saline. The second, third and fourth centrifugalizations are for 25, 15, and 15 minutes respectively, the saline being pipetted off and fresh saline added each time. Samples of blood showing any hemoglobin tinge in the supernatant saline after the third or fourth centrifugalization are discarded. The washed corpuscles are placed in the ice chest overnight, and on the following morning a 5 per cent suspension of the packed corpuscles is made up for titrations and tests. Guinea pig complement is obtained by bleeding to death from the carotid artery from three to five, preferably the latter, animals. The antisheep hemolytic amboceptor is placed in small, sealed sterile ampules after inactivation at 56° C. for one-half hour. Each batch of amboceptor is tested for its hemolytic titer with 1 c.c. of 1:10 dilution of complement from 3 to 5 guinea pigs and 1 c.c. of 5 per cent sheep cell suspension. Each batch of pooled complement is titrated against an excess (2 units) of amboceptor, the unit of amboceptor having been previously determined. One actual unit of amboceptor on the basis of the above titration lies between .35 and .4 c.c. of the dilution of amboceptor employed (1:500). For practical purposes .35 might safely be used, but .4 is taken to be the full unit, and the amboceptor is diluted 1:625 and 1 c.c. of that dilution added for the test, this being the equivalent of .8 c.c. of 1:500 dilution or two full units. As stated, for practical purposes, .35 c.c. of the 1:500 dilution is one unit and .7 c.c. two units, so that the 1 c.c. of the 1:625 dilution, employed in the reaction, represents practically three units. Ingredients are added in the order shown in the tables given. After the addition of each ingredient, the mixture is thoroughly shaken. Three antigens are employed routinely: (1) a cholesterin reinforced antigen, either human or guinea pig heart; (2) an alcoholic extract of beef, guinea pig or human heart; (3) an alcoholic extract or Noguchi acetone-insoluble lipoidal antigen. The original Citron method of using two tubes for the reaction proper, the second tube containing one-half the dose of antigen and serum used in the first tube has been followed for the first two antigens. With the third antigen only one tube with the full dose of antigen and serum is used. Each serum is controlled for its anticomplementary property with double the amount used in the test proper. Owing to the necessity of conserving reagents, the Citron method has been modified to the extent of omitting the second tube in all recent work. With the Method 1 the Citron method of degree reading is used for the first two antigens (Antigen 1 cholesterinized—Antigen 2 strongest non-cholesterinized antigen, either sample alcoholic extract or Noguchi), and merely a positive or negative reading on third antigen. With Method II the Citron method has been modified so that the weaker antigen used in the second tube is considered as though it were the same as the half amount of antigen and serum tube (back row 1 and 2) of the original method.

THE SO-CALLED DOUBTFUL OR PARTIAL WASSERMANN REACTIONS.—Charles E. Simon, Baltimore. Journal of the American Medical Association, 1919, vol. lxxii, p. 1535.

In discussing his work with some of his colleagues it was suggested that, since the Wassermann technic, even with the present system, is so time-consuming, every effort should be made to simplify it and not to lengthen the process by the introduction of any additional steps. The patients' serums are collected in the usual manner and separated from the corpuscles by centrifugation. Four-tenths c.c. are inactivated for ten minutes at 56° C., intimately mixed with 1.6 c.c. of a 2.5 per cent corpuscle emulsion (the percentage figure has reference to corpuscle mush and corresponds to 5 per cent when the mush is first diluted to the original volume of the defibrinated blood that was placed in the centrifuge tubes) and extracted for ten minutes by incubating at from 37° to 40° C. in the water-bath. The corpuscles are then thrown down and the tubes are charged with 0.2 c.c. portions of the clear supernatant fluid, to which 0.2 c.c. portions of the antigen dilutions, the complement dilution, and in the case of the control tube, of saline instead of antigen are added. After they are shaken, the mixtures are incubated at from 37° to 40° C., in the water-bath and then tested for the presence of free complement by the addition of 0.2 c.c. of amboceptor (two and a half titer doses) and 0.2 c.c. of corpuscle emulsion (of the same strength as the one employed for purposes of extraction), the tubes being returned to the water-bath and left for ten minutes, or at least until the control tubes are completely hemolyzed. The negative cases can then be read off at once and reported as such. Those tubes in which complete hemolysis has not occurred are centrifugalized and the color of the supernatant fluid is noted. If this is colorless the examination may be reported as positive without further comment, or another set of tubes may be charged with the same reagents and in the same sequence, and thoroughly shaken after the addition of each, but not incubated at all before the addition of the amboceptor and the corpuscles. If the specimen is then incubated until the control tube is hemolyzed, and complete complement fixation has occurred, as manifested by lack of any hemolysis on final centrifugation, we are dealing with a 100 per cent reaction. If partial hemolysis has occurred another set of tubes may be prepared and incubated for five minutes after adding the complement, and before testing for its fixation. If complete fixation now occurs we note the result as 91.6 per cent while partial hemolysis in this set also, but complete fixation in the ten minute specimen, would place this in the 83 per cent group. Those specimens that gave a partial reaction on first examination, after ten minutes' incubation, are now further examined, to which the author usually puts up a double set, of which the one is incubated for thirty minutes and the second for sixty minutes before adding the amboceptor and the corpuscles. If this is done, and all reagents have been functionating properly, it will be noted that every doubtful reaction will now resolve itself either into a straight negative or a straight positive reaction, the cause of the partial reaction at the end of the primary incubation for ten minutes being due, in syphilitic cases, to the presence of smaller quantities of the reacting substance which, as has been previously shown in this paper, require a longer period of time to perform the work prescribed. As we have taken as a unit that quantity of syphilitic antibody contained in 0.04 c.c. of concentrated serum, which is equal to 0.2 c.c. of the diluted and extracted original 0.4 c.c. with which we started and which requires sixty minutes' incubation in the water-bath to completely fix 0.2 c.c. of our complement dilution in the presence of 0.2 c.c. of our standard antigen dilution, we denote such a reaction as a 1 per cent reaction, whereas one occurring instantaneously, that is, without incubation, indicates a 100 per cent reaction. The intervening values may be graded accordingly.

A Modified Homocomplement Fixation Test for Syphilis.—Barton K. Thomas, Philadelphia. New York Medical Journal, 1919, vol. cix, p. 1069.

Valuable modifications to the hemolytic system of the homocomplement method are pooling sera for the determination of the hemolytic unit, the use of a light cell suspension, and finally taking, as the hemolytic unit, that amount of amboceptor which completes hemolysis in fifteen minutes rather than in twenty-five minutes. In the test itself, the use of pooled acetone insoluble antigens is of paramount importance, because the antigen is the keystone reagent in this as in every other complement-fixation test. The most valuable change in the technic of the test is the substitution of cold for heat fixation. This has not been the experience of some other workers, but this difference may be explained by the increased period of fixation adopted by us. The use of sera with a complement content of variable quantity is theoretically not a part of an ideal system, but practically the influence of this variation is of little importance, because active sera in moderately large amounts are used. In the great majority of instances with such amounts more than enough specific antibody is present to deviate all of the complement with the routine antigen excess. Noguchi has shown that unheated syphilitic serum from an active luetic patient contains one antibody-fixing unit to every .008 c.c. of serum. Therefore .2 c.c. of this patient's serum would contain twelve antibody-fixing units. In addition, although syphilitic sera in the majority of instances contain active complement, there are fewer specimens from luetics with a hypercomplementary activity than from nonluetics. These two properties of specific sera reduce the possibility of error from hypercomplementosis. It may be stated without reserve that the homohemolytic method for the diagnosis of syphilis has virtually become an essential adjunct to the serologic tests for lues. This method merits this place on account of its features of simplicity of equipment, ease with which the component parts of the test are obtained and the remarkable degree of accuracy noted in the results—an accuracy that is not exceeded by any other single method.

THE USE OF THE COLLOIDAL GOLD TEST IN PUBLIC HEALTH WORK.—Walter E. Zielinski, Buffalo, N. Y. New York State Journal of Medicine, 1919, vol. xviiii, p. 195.

As an index of pathologic change in the cerebrospinal fluid, the colloidal gold reaction is more delicate than any other test here employed. Normal spinal fluid usually causes no reduction of the colloidal gold. A slight reduction in any of the dilutions is of no diagnostic import, and may occur in normal spinal fluids. Cases of tabes and cerebrospinal lues give a typical colloidal gold curve in the luetic zone. Although in tabes the intensity of the curve is usually greater, it is not sufficiently constant to be of diagnostic value between the two conditions. In paresis the colloidal gold test is sufficiently frequent and characteristic to warrant the term, "Paretic Curve," and is of great diagnostic value. In meningitis the colloidal gold curve normally occcurs in the higher dilutions and is probably of value in the diagnosis of doubtful cases. The colloidal gold test is more delicate than the Wassermann test. Spinal fluids from luetics have given a colloidal gold luetic curve with a negative Wassermann. However we have never observed a normal colloidal gold curve with a positive Wassermann in the spinal fluid. No spinal fluid test (except the presence of bacteria) is specific. Every test is simply that much cooperative evidence and should be combined with the history of the case and the clinical findings. The presence of red blood cells or plasma in the spinal fluid often vitiates the result of the test. Since the whole test is based on the interrelationship of the coagulable proteins, albumin and globulins, the former protecting the colloidal gold, the latter precipitating it, the necessity for accuracy, cleanliness, and attention to significant detail is seen in the colloidal gold test in order to secure reliable, consistent and comparable results.

STUDY OF THE CEREBROSPINAL FLUID IN THE DIFFERENT PERIODS OF SYPHILIS.—Dr. Georges Cornaz, Lausanne. Journal of Nervous and Mental Diseases, 1919, vol. xliv, p. 282.

The author's observations enable him to confirm how frequent and early is the extension of the syphilitic infection into the meninges, since in the 35 per cent by the cases of hard chancre the number of leucocytes was already increased at a time when the cutaneous or mucous manifestations were still totally absent or at least could not be demonstrated by our means of investigation. It is the lymphocytosis which at first betrays the modifications in the fluid, when the quantity of albumin is still normal and when the generalization of the infection has not yet been demonstrated by the Wassermann reaction. In the exanthematous stage 14 per cent of the fluids gave a complement fixation. This figure is met with again much the same (13 per cent) in the cases of large condylomata when, among the patients showing mucous plaques, the fluid Wassermann was positive only once in 25 cases. This curious difference is not easily explained. Are there anatomico-histologic conditions favoring the passage in the fluid of bodies capabale of becoming fixed in the antigen especially among the carrriers of the condylomata or indeed do the condylomata result in a more abundant formation of these bodies? The modifications of the fluid seem at least to be in accord with the reactions of the skin and we may ask whether we have not here a question of the phenomenon of allergia. This conclusion would support the idea which Professor Dind has been one of the first to defend, that allergia is an essentially cutaneous phenomenon. The condylomata, cutaneous lesions, would provoke a violent reaction of the organism when the lesions of the mucous membrane alone would not excite the individual to defense in the same degree. As soon as the syphilis localizes itself in the central nervous system, the cerebrospinal fluid constantly presents important modifications and it is of great value in investigation for fixing the diagnosis or for controlling the course of treatment. The Wassermann reaction should be specially made in these cases for it is relatively frequent that it is positive in the fluid and negative in the blood. This little study will make evident, the author hopes, the utility of practicing lumbar puncture upon syphilitics. The operation presents besides no danger. In many hundred cases of punctures he has had no serious accident to record. The patients rarely complain of vertigo or headache, but it is absolutely necessary that those who have undergone puncture should lie flat without a pillow for 24 hours. The quantity of fluid withdrawn should be as little as possible. Five cubic centimeters are enough for the enumeration of lymphocytes in the cell of Nageotte, the measurement of albumin and the Wassermann reaction.

THE METHOD OF OBTAINING CEREBROSPINAL FLUID BY PUNCTURE OF THE CISTERNA MAGNA (CISTERN PUNCTURE).—Paul Wegeforth, James B. Ayer and Charles R. Essick, Baltimore. American Journal of the Medical Sciences, 1919, vol. clvii, p. 789.

Puncture through the occipitoatlantoid ligament offers a convenient method for obtaining cerebrospinal fluid from laboratory animals; it has also been found more satisfactory than lumbar puncture in obtaining fluid at the autopsy table. After study of the anatomic relations of the cisterna in man, and after numerous successful punctures on the cadaver, the authors believe that the operation in skilled hands is a safe one for clinical use. They do not wish to minimize the possible harm which can result from such puncture; on the other hand, they are convinced that the technic is not difficult and that practice upon the cadaver will be convincing on this point, without much preliminary study the operation should not be performed. Clinically, the procedure should prove useful (1) in reaching the upper fluid reservoirs of the central nervous system after blockage of the spinal subarachnoid space; (2) in combination with lumbar puncture for irrigation of the spinal subarachnoid space; and (3) in affording a method whereby specific therapy could be given more efficiently in early meningitis.

SOME PRACTICAL POINTS IN THE DIAGNOSIS OF SYPHILIS OF THE NERVOUS SYSTEM.—Edward Livingston Hunt, New York. Medical Record, 1919, vol. xcv, p. 391.

The history in syphilis is not so important as one has been led to believe from textbooks and teaching. The man who has had syphilis does not wish to realize it, and often is unwilling to admit it. The practical points in the clinical examination of the syphilitic are: (1) The condition of the pupils; (2) the condition of the reflexes; (3) the condition of the circulation. Of these three, by far the most important is the condition of the pupil. In examining the pupil, look for three things—size, contour, and reaction to both light and accommodation. The pinpoint pupil is much more suggestive than the dilated. Markedly unequal pupils are even more suggestive. The contour of the pupil is something which the neurologist looks for but which the general practitioner is prone to neglect. Of course, we know what contour means—the outline of the pupil. In the normal individual this should be smooth and even. Syphilis causes rough and unequal edges. Apparently the poison causes a breaking or bulging out of the line of the pupil. Perhaps the most important of all these three eye signs is that of the reflexes. A very sure, almost definite, sign of syphilis is the failure of the pupil to react to light. The condition of the tendon reflexes is of equal importance with that of the pupil. Changes in the reflexes do not, however, occur as early, nor progress as fast. The important reflex affected in syphilis is the knee jerk. We must bear in mind not only that it may be absent, but also that it may be exaggerated, or that the two knee jerks may be unequal. The condition which an examination of the circulation reveals, is of equal importance with the one shown by the reflexes and with that of the pupil. The heart may be enlarged, there may be valvular lesions, especially aortic, and there may be a dilatation of the aorta, or even an aneurysm. There may be very high blood pressure, or there may be palpable thickening of the arteries. The author calls attention to the laboratory analyses which can and should be made in the examination of syphilis of the nervous system. They may be classified under two headings—those of the blood, and those of the spinal fluid. Of the two, undoubtedly the examination of the spinal fluid is the more important. The cell count is not considered of so much importance as formerly. All we can tell from a large cell count is that there is an inflammation, an irritation, an abnormal condition, in the spinal canal. This may be due to syphilis, mechanical disturbances, or a meningeal infection. A very important test is the colloidal gold. It is difficult to make, it requires a great deal of time, and the solution easily deteriorates. The gold test is the one of all most to be relied upon. When the cell count, the Wassermann, and the gold test are taken together, they form three arguments which the author considers more valuable and more infallible than any other three—either the history, the clinical examination, or the x-ray pictures. The x-ray is of value because it reveals the enlarged aorta, the beginning aneurysm, the dilated heart and occasionally, some specific condition in the head. Finally, the one important point in diagnosing syphilis of the nervous system is to get as much data as possible and then to correlate it properly. Weigh the history with the clinical findings, with the laboratory report, and the x-ray pictures. Do not stop at any one of the four, or at any three of the four.

A Brief Resume of Certain of the Stigmata of Late Hereditary Syphilis.—B. Barker Beeson, Chicago. Medical Review of Reviews, 1919, vol. xxv, p. 158.

Strictly speaking, none of the lesions mentioned afford absolute evidence that the case at hand is one of syphilis. When two are simultaneously present as interstitial keratitis and the characteristic notched upper median incisors then the diagnosis of lues would be practically certain. Hutchinson's triad also speaks for specific disease in the strongest terms. From the frequency with which it has been associated with a positive Wassermann and also because it occurs more often than the other stigmata, the author is inclined to regard interstitial keratitis as the most important stigma of late hereditary syphilis. Following interstitial keratitis the author places the Hutchinson teeth, which are of great value even when found alone. Unfortunately they are but rarely observed. The sabre blade tibia is another extremely important stigma, almost always associated with syphilis. There are certain stigmata: (a) interstitial keratitis, (b) Hutchinson teeth, and the (c) sabre-like tibia, which are of prime importance in the diagnosis of lues. These stigmata are only very rarely present in other conditions. Interstitial keratitis frequently coincides with a positive Wassermann reaction. The other two have also been observed with a similar complement-fixation test. Whenever observed, any of the stigmata which have been mentioned, but more especially the last three should lead to a searching investigation for the presence of syphilis. The presence of interstitial keratitis, Hutchinson teeth or sabre tibia should cause the case to be considered as specific, unless strong contradictory evidence is presented.

CONTROL OF SYPHILIS.—R. C. Jamieson, Detroit, Mich. New York Medical Journal, 1919, vol. cix, p. 984.

The author emphasizes the supreme importance of the early diagnosis of syphilis no matter what the manifestation may be, whether genital, dermal, internal, for the best results of treatment can only be obtained if treatment can be instituted at once. This applies not only to the general practitioner, but also to all the specialists, the genitourinary man, the gynecologist, obstetrician, dermatologist, ophthalmologist, rhinologist, internist, surgeon, and neurologist. Lesions may be encountered by any of these specialists and it is strictly up to them to make a prompt diagnosis—not a diagnosis that is satisfied to call a person free of syphilis with one negative Wassermann, in spite of positive evidence, but one which definitely proves or disproves the presence of syphilis. The second point deserving emphasis is prophylaxis—a point which speaks for itself when we remember that the incidence of venereal disease in the army in France was less than it was at home on account of the prophylactic measures being strictly enforced as well as the other reasons mentioned above. Prophylaxis actually protects in 90 per cent of the cases if used early enough. Scrupulous observance of prophylactic measures as well as cleanliness together with a more rational understanding by the laity of the modes of contagion will go a long way to curb the spirochete. Prohibition has also helped, as a man who is not under the influence of alcohol will be far more likely to take proper precautions. The author does not believe prostitution, broadly speaking, can ever be eradicated, but of the two, clandestine and public, while both are dangerous, the recognized prostitute can be kept under more strict surveillance than the occasional prostitute.

ON SILVER SALVARSAN.—Gennerich. Deutsche medizinische Wochenschrift, 1918, vol. xliv, p. 1247.

This combination is said to contain arsenic in smaller proportion than the older preparations—from a third to a half the strength. Nevertheless it is said to be extremely powerful and superior in therapeutic efficacy to the older and stronger arsenicals. It apparently is superior to the latter in effecting a radical cure of the disease in the first six months of an infection. So far as changing the seroreaction is concerned, it transforms a positive to a negative within the first month of the early case. The addition of mercury during these periods does not seem to be indicated. Furthermore the lowered toxicity of silver salvarsan in comparison with that of the older arsenicals is specially remarkable when considered in association with its increased therapeutic efficiency. The author has made over 1000 individual injections of silver salvarsan and the only untoward results were slight cyanosis in two patients. The toxicity of the older salvarsans is due probably to several factors, as oxidation before or during injection, defective elimination, presence of diseases of the alimentary canal, the synchronous use of mercury, the direct action of the arsenic on the ehpatic cell, etc., but apparently none of these factors is in evidence when silver salvarsan is used.

DETERMINATION AND DISTRIBUTION OF ARSENIC IN CERTAIN BODY FLUIDS AFTER THE INJECTION OF ARSENOBENZOL, SALVARSAN AND NEOSALVARSAN.—C. N. Myers, Washington, D. C. Public Health Reports, 1919, vol. xxxiv, p. 881.

This method, essentially a modification of the Lockemann method, is applicable for the determination of small amounts of arsenic in organic material. It gives excellent results when applied to urine, blood, serum, etc. The method gives best results when applied to samples or aliquots containing 1 to 7 parts per million. All samples should be weighed, rather than measured, when analysis is to be carried out. The amount of arsenic found in these fluids was largest in the serum and least in the spinal fluid.

IMPORTANT PRECAUTIONS IN ADMINISTERING ARSPHENAMINE AND NEOARSPHENAMINE.—Public Health Reports, 1919, vol. xxxiv, p. 1131.

Experience has shown that the untoward results occasionally associated with the administration of arsphenamine are due in a large measure to the use of too highly concentrated solutions of the drug, to too rapid administration, and to insufficient care in rendering the solution slightly alkaline. The reader, therefore, may be interested in studying the following instructions just issued to medical officers of the Public Health Service regarding the administration of arsphenamine and neoarsphenamine. Careful observance of the precautions here described will reduce the number of reactions from the use of these drugs. The ampule, before opening should be immersed in 95 per cent alcohol for fifteen minutes in order to detect any crack or aperture not primarily recognizable. (Should such a breach be discovered, the contents of the ampule should be discarded.)

Arsphenamine. (1) Solution.—Cold, boiled, freshly distilled water should be used in all cases except in the case of "arsenobenzol" made by the Dermatological Research Laboratory, in which case hot water is required. No more solution should be prepared at one time than can be given in 30 minutes.

(2) Neutralization and alkalinization of the above solution.—With a graduated pipette or burette add 0.9 c.c. of normal NaOH for each 0.1 gm. of the drug (i.e., 5.4 c.c. for each 0.6 gm.). The alkali should be added all at once and should quickly convert the acid salt solution of arsphenamine into the alkaline salt solution, or the disodium of salt of the arsphenamine base. (The solution of arsenobenzol, which is hot, should be cooled before adding the alkali.) This represents slightly more alkali than just enough to redissolve the precipitate formed by the addition of this reagent. The alkali should be standardized against normal acid. Normal NaOH is a 4 per cent solution of the C. P. product. However, if made on the basis of weight, it may be considerably less than this strength, hence the necessity for titration. It could be made up in amount sufficient for a month's use if kept in a well-stopped bottle and exposed to the air for only a few seconds at a time when using the solution. It should be kept in a bottle that has been used for NaOH solution for some time, so that all action it causes in the glass will have occurred. Where it is impossible to have this made up at the station, it will be furnished upon request from the Hygienic Laboratory. Should the NaOH solution become cloudy or contain a precipitate, it should be discarded.

(3) Concentration of the drug.—It is desired to emphasize the fact that the concentration of the drug should not be greater than 0.1 gm. to 30 cc.. of final solution. The practice of using concentrated solution is not only in direct conflict with the instructions on the circular, but carries a distinct hazard to the patient.

(4) Method of injection.—The gravity method only should be used. Where several patients are to be injected from the same solution, the container for the solution should be graduated. If not already graduated, this can be done in a few minutes by sticking on a strip

of adhesive plaster and marking the graduations on this. A convenient way to do this is to have each mark represent 30 c.c., with a long mark for each 180 c.c.; then, if the volume is made up so that each 0.1 gm. of drug is contained in each 30 c.c., the doses can be given accurately. It is a great convenience to have a glass stopcock near the glass tubing, which serves as a window just above the needle in order to control the rate of injection. If no stopcocks are at hand, the rate can be controlled by the size of the needle and the height of the column of fluid. A no. 18 or 20 B. & S. gauge is the best sized needle.

(5) Rate of injection.—Operators should pay particular attention to the rate of administration and in no case should it exceed 0.1 gm. of drug (30 c.c. of solution) in two minutes. This point is especially emphasized because it is believed that excessive rapidity of administration accounts for more unfavorable results in the use of arsphenamine than any other one thing.

Neoarsphenamine.—The principal precautions to be observed in the administration of neoarsphenamine are:

1. Only a single ampule should be dissolved at a time. This drug must not be dissolved in bulk to be given to a series of patients.
2. Cold water only should be used.
3. The dilution should not be stronger than 0.1 gm. of the drug in 2 c.c. of freshly distilled water.
4. A very small needle should be used, and the time of injection of the dose should not be less than five minutes.

VASODILATORS IN THE INTRAVENOUSS TREATMENT OF SYPHILIS WITH ARSPHENAMINE.—George Edward Barnes, Herkimer, N .Y. Boston Medical and Surgical Journal, 1919, vol. clxxx, p. 558.

Even when an acutely acting vasodilator like nitroglycerin is used, there is good reason to use, in many cases, remedies which will quite continuously maintain a state of normal tension of the blood vessels. Many syphilitic patients, through the emotional reaction aroused by their concern over some aspect of their disease, have abnormally contracted blood vessels, and this condition must be a serious obstacle to the proper diffusion of arsphenamine through their tissues. There is need often of such drugs as gelsemium, bryony, cannabis, sumbul, pulsatilla, lupulin, cramp bark, solanum, conium, ailanthus, cyripedium, sparteine, cactus, cimicifuga, etc. Among these drugs sparteine, conium, and cramp bark are especially good for opening up the capillaries. Thyroid extract and potassium iodide also open up the capillaries, but they are not sedative. Sparteine is expensive and conium loses its activity after eighteen or twenty-four months, but both are excellent. In order to dilate the veins so that the needle can be inserted with greater ease, vasodilators are also sometimes indicated. Nitroglycerin may be tried. It is usually sufficient. It is most conveniently taken in tablet form, chewed up, dissolved in saliva, and swallowed. Such an active drug, however, should not be used until it has been ascertained that the particular patient under treatment does not have the nitritoid reaction, caused by the arsphenamine or by the nitrites in the distilled water used. An important point to be observed in order to have the veins relaxed as well as possible, in some cases, at time of venipuncture, is the administration of drugs that have a sedative effect on the whole nervous system and the blood vessels, as those mentioned above. A warm bath is good. A hypodermic injection of morphine sulphate is doubtless the most efficacious. Whatever reflex contraction of the veins may be produced by the puncture of the needle would also tend to be diminished by the above treatment.

EXFOLIATIVE DERMATITIS DUE TO ARSPHENAMINE.—Joseph R. Latham, Belhaven, N. C. Journal of the American Medical Association, 1919, vol. lxxiii, p. 14.

A fatality followed a therapeutic dose of arsphenamine, the equivalent of less than three grains of metallic arsenic. Diarrhea and vomiting were absent during all stages of the intoxication. Nephritis was not a marked feature at any time, and appeared only at the end. There was apparently a decided affinity of the poison for the skin or for the trophic nerves supplying it. From first to last all the toxic symptoms may logically be ascribed to impairment of skin function. Arsenic was persistently present in the urine. This was remarkable in the absence of accompanying renal inflammation. There was a high leucocytosis and eosinophilia, the latter related closely to the patient's resistance. The height of the leucocytosis followed that of the fever. Arsenic was found at necropsy in every tissue in which it was sought.

REFLECTIONS ON THE THERAPY OF SYPHILIS.—Simon, Paris. Journal de Médecine et de Chirurgie Pratiques, 1919, xc, p. 161.

Our treatment of syphilis is now in full revolution. Fournier's old rules, once classical, are now attacked on all sides. Especially is there lack of harmony in the treatment of the latent case. For some the disease, treated or not, is chronic and requires modifications according to its duration. A syphilis ten years old should have a management apt for that age. Some of us lean on the seroreaction and would first lower and then suppress the positive find. But of Wassermann vagaries there is no end and one man finds that if a negative case is treated as though it were positive the reaction undergoes perturbations. Milian to whom reference is made in other words has called attention to the possibility of reactivation of the Wassermann. Otherwise interpreted one should not be content with the negative single Wassermann but continue to make tests. Even if there is no reactivation in a blood test we should not be content, but test the cerebrospinal fluid. Even that is not final for if there chance to be an exudate anywhere in the body that fluid should also be tested. In such cases a pleural effusion may give a Wassermann positive after blood and spinal fluid have given a negative result. These vagaries make us a little skeptical about the Wassermann as a whole, and certainly as a guide to treatment. In supposed latent syphilis with all evidence of the disease absent and in cases used as controls repeated tests show such irregularities that one does not have to compare two cases, for in one patient tested at different times the dissonance is equally in evidence. We may see a positive reaction become spontaneously negative and vice versa. This behavior can sometimes be explained by the course of the disease. A long latent syphilis may spontaneously become active with change of reaction. The practice of injecting arsenicals to prevent the reawakening of a latent syphilis is questionable and there should be active rather than latent treponemata to combat when we give spirillocides. In regard to the criterion of cure of Vernes the author admits the experience of the latter but thinks it insufficient to form laws.

At present we have nothing to take the place of the Wassermann and can not go back to the generalizations of Fournier. Does the Wassermann tell us how to treat a patient as well as when? There is little want of harmony in primary syphilis. Here as soon as we find spirochetes in the primary lesion we examine for albumin and if this is absent push arsenic and mercury both. So much drug given so often over such and such interval is the procedure with some of us. Others fear to develop a strain of treponemata which is drug resistant and would not provoke the organisms by too intensive courses. Better according to this view is a small dose repeated over long intervals with pauses. There is a practical objection here for the patient easily slips from control. Other objections lie in the arsenic intolerance exhibited by many patients as shown by the so-called nitritoid crises. In the present state of our knowledge the author would not trust a constant negative Wassermann too far in the first years of the disease, but would give treatment in medium doses with suitable pauses. In the opposite case of a constant positive reaction without clinical manifestations the need for intensive treatment is also absent but he would give slowly increasing doses also with pauses.

EXPERIENCES WITH NEODIARSENOL (CANADIAN NEOARSPHENAMINE); 241 INJECTIONS WITHOUT ILL EFFECTS.—Hermann Goodman, Camp Las Casas, Porto Rico. Medical Record, 1919, vol. xcv, p. 637.

Neodiarsenol was injected 241 times in 100 cases. With proper care in the preparation of the glassware, freshly distilled water that had been boiled and cooled to room temperature, and the patient prepared, the injections of neodiarsenol were not attended proportionately with any greater number or kind of reactions than the injections of 147 doses of arsenobenzol (Schamberg) which were administered to 59 women during the same period.

Serologic Cure (?) in the Light of Increasingly Sensitive Wassermann Tests.—Udo J. Wile and Clyde K. Hasley, Ann Arbor, Mich. Journal of the American Medical Association, 1919, vol. lxxii, p. 1526.

It appears to the authors that in a total of thirty-nine cases, treated over the period of eighteen months, only six cases have become serologically negative with the ice-box test, as against twenty-two, or more than 50 per cent, which became apparently negative with the old test. The modern methods of carrying out the Wassermann reaction are today, under all conditions, far more sensitive than those which were used in the early days of serologic examination. Each year some refinement of the technic brings to light more and more positive cases which, under previous conditions, would have been negative, and it seems quite reasonable to us to predict that the last word on the subject is yet far off. It is even justifiable to assume that within a short time a test more sensitive than that carried out in the ice box may be elaborated. When one compares the relative sensitiveness of older tests with those employed today, and the ever increasing refinements, it becomes apparent that at best our laboratory methods are crude means to detect chemical and physicochemical changes taking place in the cells of the body after infection. As a diagnostic aid, the positive Wassermann reaction still stands as our greatest aid and a tremendous step forward in the uncovering of syphilis. It has long been taught, and until recently the authors shared with others the belief, that the goal to be attained in the treatment of syphilis is the conversion from a positive to a negative phase in the blood test. They are fast being converted to the view that, except in the small group of early cases in which positive tests are never elicited and the cases are aborted, to attempt this end is, as it were, chasing a shadow. Until more is known about the nature of this reaction, as to whether it is caused by antibodies or immune substances, it seems to us that there is equally less justification to attempt or to expect well-established positive cases to become permanently negative. They are convinced that in the presence of an intensive therapy, a positive test does not necessarily mean living spirochetes and potential syphilis any more than a positive tuberculin test in an individual who has had tuberculosis would indicate the presence of living tubercle bacilli. With the ever increasing discrepancies reported with each refinement of the Wassermann test; with the ever increasing number of permanently positive cases, previously regarded negative, it appears that as a guide to therapeusis, the Wassermann reaction does not have a leg to stand on. We stand today, with regard to the criteria of the treatment and cure of syphilis, as did the syphilologists of the pre-Wassermann day. Until recently the authors have taught, as have all others, and have impressed on patients, that treatment must be continued until the blood no longer shows evidences of syphilis. Undoubtedly they, as all others, have passed, as cured, cases which have been recorded as negative, depending on the degree of delicacy of the test at the time. They do not feel that these cases are necessarily not clinically cured, although modern tests would show many surely as positive. Whatever intensive treatment has been directed toward the eradication of the Wassermann reaction has undoubtedly been well directed toward the eradication of the disease. In the light of our real ignorance of the nature of the reaction, particularly in the interpretation of late persistent tests, they submit that serologic and clinical cure are not necessarily parallel. Energy of treatment directed toward the end of attempting to make a persistent positive react negative may well be not only useless but misdirected.

THE ADEQUATE TREATMENT OF SYPHILIS.—J. J. Seelman, Milwaukee. Wisconsin Medical Journal, 1919, vol. xvii, p. 438.

Syphilis is a far more prevalent disease than is usually supposed. There will be a considerable increment of cases of active syphilis after the war. Because of the well-developed relative immunity of the human race to syphilis, the majority of infected persons become mere spirochete carriers, with Wassermann negative blood, and never develop any symptoms which are definitely referable to the disease. In these cases there is usually no history of well-defined primary or secondary lesions, because immunity factors prevent their occurrence. In only a small proportion of persons who become infected, immunity resistance is on a sufficiently low level to admit the development of definite primary or secondary lesions. Wherever recognized in the primary or secondary stage, the patient should, whenever possible, receive intensive and sustained treatment. For intensive treatment daily or bi-daily, intravenous arsphenamine injections are preferable to the weekly injections, provided, of course, that they can be tolerated. In tertiary cases the intensive treatment is only exceptionally indicated. In many cases it may prove harmful. These cases should all be treated according to individual requirements. In every case of syphilis a lumbar puncture should be made. In primary and secondary cases this should be done after treatment has been completed and before the patient is discharged as cured, and in tertiary cases as soon as the disease has been diagnosed or is suspected of being present. If the findings are positive, the patient should at once be turned over to the specialist.

REGULATIONS GOVERNING THE SCIENTIFIC RESEARCH FUND OF THE UNITED STATES INTERDEPARTMENTAL SOCIAL HYGIENE BOARD[1]

THE United States Interdepartmental Social Hygiene Board prescribes the following rules and regulations in conformity with that part of section 6, Chapter XV, Public 193, 65th Congress, which provides that the sum of $100,000 "shall be paid to such universities, colleges, or other suitable institutions as in the judgment of the Interdepartmental Social Hygiene Board are qualified for scientific research for the purpose of discovering, in accordance with the rules and regulations prescribed by the Interdepartmental Social Hygiene Board, more effective medical measures in the treatment and prevention of venereal diseases."

1. Appropriations from this fund will be made only to universities, colleges, or other suitable institutions that give satisfactory evidence of possessing a staff of scientific experts and an equipment of scientific apparatus, supplies, and resources that will guarantee that the researches undertaken will be carried out under approved scientific conditions and in conformity with scientific methods.

2. Appropriations for this fund for scientific research will be made only for definite investigations that are described by the proposers in sufficient detail to satisfy the Interdepartmental Social Hygiene Board that there is a justifiable expectation that these researches "will discover more effective medical measures in the prevention and treatment of venereal diseases."

3. The universities, colleges, or other institutions proposing researches and asking for appropriations will furnish information on the following subjects:

(*a*) Name of institution requesting appropriation.
(*b*) Name, office, and address of official representative of this institution.
(*c*) Title concisely descriptive of research proposed.
(*d*) Laboratory in which research is to be carried out.
(*e*) List of more important scientific publications from this laboratory.

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[1] See section 6, Chapter XV, Public No. 193, 65th Cong., Army appropriation bill of July 9, 1918.

(*f*) Name and concise statement of the scientific training of the laboratory chief or director, or other individual responsible for the scientific policy of the laboratory.

(*g*) Laboratory staff, giving names, degrees, etc.

(*h*) Laboratory equipment and facilities, with a concise statement indicating scientific and working capacity of the laboratory, and cooperating laboratories, departments and agencies.

(*i*) Description of research proposed; outline plan in sufficient detail to show clearly its scientific character and justify the expectation that it will discover ''more effective medical measures in the prevention and treatment of venereal diseases.'' Include references to important scientific literature bearing on research proposed.

(*j*) Probable cost. Give general items covering the necessary equipment and supplies, with an estimate of the probable cost of preparing and printing a report. Should not include the salaries of scientific investigators, but may include salaries for technical assistants.

(*k*) Will this institution be able to carry on the research proposed if it receives no financial aid from the Interdepartmental Social Hygiene Board?

4. Universities, colleges, and other institutions asking for appropriations will furnish the board with a budget made out on forms supplied by the board and will make an accounting of their disbursements in conformity with the rules of the Comptroller of the Treasury of the United States Government.

APPROPRIATIONS TO JUNE 26, 1919

The United States Interdepartmental Social Hygiene Board, through its Executive Secretary, Dr. T. A. Storey, 1800 Virginia Avenue, N. W., Washington, D. C., announces the following appropriations made from the Scientific Research Fund and Educational Research and Development Fund of the Board, up to June 26, 1919.

Appropriations have been made from the Educational Research and Development Fund of the United States Interdepartmental Social Hygiene Board to the following institutions for the purpose of organizing or completing the organization within those institutions of Departments of Hygiene, the curricula of which shall include ''courses and conferences in informational hygiene, and courses, conferences and training in the application of hygiene, emphasizing with appropriate and due proportion and proper tact and persistency the serious importance of the venereal diseases, their causes, carriers and prevention, and emphasizing at the same time the other important facts and applications of general hygiene, individual hygiene, group hygiene and intergroup hygiene:"

Los Angeles, Calif., State Normal School.
Natchitoches, La., Normal School.
Maryland Normal and Industrial School (colored).
Maryland State Normal School.
Michigan State Normal School.
Winona, Minn., Normal School.
University of New Mexico.
Valley City, N. D., Normal School.
Reed College, Portland, Oregon.
Bellingham, Wash., Normal School.
University of Utah.
Alcorn, Miss., A. & M. College (colored).
Woman's Medical College of Pennsylvania.
Harvard University.
University of Missouri.
Colorado State Teachers College.
New York State Teachers College.
Cornell University.
University of South Carolina.
Northwestern University.
University of Pennsylvania.
Cheney, Wash., State Normal School.
Milwaukee, Wis., Normal School.
Indiana University, Bloomington, Ind.
University of North Carolina.

An appropriation from this Fund was made to a committee of Psychologists under Dr. J. R. Watson of Johns Hopkins "for the purpose of investigating the informational and educative effect upon the public of certain motion picture films used in various campaigns for the control, repression and elimination of venereal disease."

Appropriations have been made to the following institutions from the Scientific Research Fund of the Board for the purpose of discovering more effective medical measures in the prevention and treatment of venereal diseases.

Leland Stanford Junior University Medical School.

"Investigation into more effective treatment in acute and chronic gonorrhea." Under the direction of R. L. Rigdon, M.D., Clinical Professor of Genitourinary Surgery, and A. B. Spalding, M.D., Professor of Obstetrics and Gynecology.

''The permeability of the meninges to antisyphilitic drugs—an attempt to increase their permeability.'' Under the direction of H. G. Mehrtens, M.D., Clinical Professor of Neurology.

''Investigation into more effective methods of treating syphilis.'' Under the direction of H. E. Alderson, M.D., Clinical Professor of Dermatology.

University of Michigan, College of Medicine and Surgery.

''A research for an improved method of demonstrating the spirochaeta pallida in human tissues.'' Under the direction of A. S. Warthin, M.D., Professor of Pathology.

Johns Hopkins Medical School.

''Development of new synthetic drugs for the treatment of gonorrhea.'' Under the direction of Dr. E. C. White, Experimental Chemist to Brady Urological Institute.

''Manufacture and investigation of a series of new organic compounds in the treatment of syphilis.'' Under the direction of Dr. D. M. Davis.

''Manufacture and investigation of a series of penetrating organic dyes in the treatment of chancroids.'' Under the direction of Dr. E. O. Swartz.

''Experimental study of various methods of early treatment of venereal infection with the object of developing simpler technic, more efficient and less expensive drugs.'' Under direction of Dr. William Jack.

University of Wisconsin Medical School.

''An attempt to prepare mercurial and arsenical compounds which have a predilection for the central nervous system, in the hope of finding drugs more useful than any known in the treatment of syphilis of the central nervous system.'' Under the direction of Dr. A. S. Loevenhart, Director of Laboratory.

University of Nebraska College of Medicine.

''Investigation relative to the development of an internal urinary antiseptic,'' and ''Investigation of the value of certain anilin dyes in the treatment of gonorrhea.'' Both under the direction of E. G. Davis, M.D., Director of Pathological Laboratory.

St. Louis University College of Medicine.

''Studies in infection by gonococci.'' Under the direction of R. A. Kinsella, M.D., Director of the Department of Experimental Medicine.

Woman's Medical College of Pennsylvania.

''A serological study of syphilis in pregnant women and new-born children with special reference to the efficacy of the accepted methods of syphilitic treatment.'' Under the direction of Bertha M. Meine, M.D., Director of Research Department.

Washington University School of Medicine.

"The laboratory (biological) investigation of the latent syphilitic as a 'carrier.'" Under the direction of Martin F. Engman, M.D., Professor of Dermatology.

"A study of hereditary transmission of syphilis." Under the direction of P. C. Jeans, M.D., Instructor and Associate in Pediatrics, and Jean V. Cook, M.D., Associate in Pediatrics.

Cornell University Medical College.

"Serological study of the gonococcus group." Under the direction of John C. Torrey, Ph.D., Professor of Hygiene.

Jefferson Medical College of Philadelphia.

"A series of studies for the recognition and diagnosis of treponema pallidum in venereal diseases, and the effect of various drugs and materials as germicidal agents against treponema pallidum." Under the direction of Randle C. Rosenberger, M.D., Professor of Hygiene and Bacteriology.

Yale University Medical School.

"Effect of anilin dyes, particularly Gentian Violet, on the gonococcus with reference to the growth of the organism in media containing the dye, and with reference to the effect on organisms in tissue (therapeutic effect)." Under the direction of J. M. Flint, M.D., and J. W. Churchman, M.D., Professors of Surgery.

"An intensive study of methods for the isolation and identification of the gonococcus with a view to the determination of the homogeneity or heterogeneity of strains and their etiological relationships." Under the direction of George H. Smith, M.D., Assistant Professor of Department of Pathology and Bacteriology.

"The demonstration of syphilitic nature of unusual lesions encountered at the postmortem table." Under the direction of M. C. Winternitz, M.D., Professor of Pathology and Bacteriology.

Union University Medical Department, Albany.

"For studies on the nature of the Wassermann reaction." Under the direction of Thómas Ordway, M.D., Dean and Associate Professor of Medicine.

"An attempt to produce generalized infection in lower animals with treponema pallidum or gonococcus." Under the direction of George S. Graham, M.D., Professor of Pathology, and W. M. Baldwin, M.D., Professor of Anatomy.

University of Minnesota Medical School.

"A study of the permeability of bacterial membranes, particularly the organisms of venereal disease." Under the direction of W. P. Larson, M.D., Chief Department of Bacteriology and Immunology, and J. F. McClendon, Ph.D., Associate Professor of Physiology.

"Investigation of the chemical and physical properties of the cerebrospinal fluid in the luetic and non-luetic." Under the direction of L. G. Rowntree, M.D., Chief, Department of Medicine, and Charles E. Nixon, M.D., Instructor in Nervous and Mental Diseases.

"Investigation of phenol alcohol derivatives in relation to their antisepsis and chemotherapy of the gonococcus and spirochete." Under the direction of A. B. Hirschfelder, M.D., Chief, Department of Pharmacology, and H. G. Irvine, M.D., Assistant Professor of Dermatology and Syphilis.

Harvard University Medical School.

"An investigation of the properties contributing to the toxicity of arsphenamine, neoarsphenamine and analogous products." Under the direction of Reid Hunt, M.D., Professor of Pharmacology.

The United States Interdepartmental Social Hygiene Board is composed of—

Carter Glass, Secretary of the treasury,
Newton D. Baker, Secretary of War,
Josephus Daniels, Secretary of the Navy,
Lt. Col. W. F. Snow, Medical Corps, U. S. A.
Lt. Comdr. J. R. Phelps, Medical Corps, U. S. N.,
Asst. Surg. Gen. C. C. Pierce, U. S. Public Health Service.
Thomas A. Storey, Executive Secretary.

WORK OF THE DIVISION OF VENEREAL DISEASES OF THE UNITED STATES PUBLIC HEALTH SERVICE

June 1, 1919.

Editor, American Journal of Syphilis.

Dear Doctor:

When the Chamberlain-Kahn Act created the Division of Venereal Diseases in the United States Public Health Service and the great work of venereal disease control was inaugurated, the plan of procedure formulated was grouped under three headings, as follows: 1, Medical Measures; 2, Law-enforcement Measures; 3, Educational Measures.

The EDUCATIONAL measures include the dissemination of information by leaflets, lectures, exhibits, moving pictures, stereopticon views, and other means, among industrial plants, commercial institutions, clubs, libraries, community centers, schools, churches, the home, and every walk of life.

The LAW-ENFORCEMENT measures include encouragement of the closing of restricted districts; stimulating enforcement by state and municipal officials of laws and ordinances directed against prostitution in all its phases, the establishment and management of institutions for the rehabilitation of venereally infected persons, and the commitment to institutions of venereally infected feeble-minded persons; urging the adoption and enforcement of laws and ordinances compelling the reporting of the venereal diseases, the prohibiting of quack advertising, and the sale of venereal disease nostrums; and other measures designed to prevent the spread of the venereal diseases.

The MEDICAL measures include the establishing of clinics; securing hospital facilities for venereally infected persons; making available laboratory facilities for the scientific diagnosis of venereal diseases; securing wide distribution of arsphenamine or similar products; obtaining the support of the entire medical profession by the reporting of their cases to the State Board of Health and the treating of venereally infected persons, in accordance with the best modern methods; securing the cooperation of druggists in refusing to dispense venereal nostrums and directing prospective purchasers of such remedies to venereal disease clinics, or reputable physicians; securing the cooperation of dentists and nurses in their respective fields of practice; and enlisting the interest and services of all medical, dental, and pharmaceutical schools, societies, and journals.

Under Medical measures, the campaign was begun with the advertising media of the country. The 20,000 newspapers and magazines carrying advertising were appealed to for cooperation, with the result that up to the present, according to agreement cards received, and clippings made, approximately 140 only, or less than one per cent, are still carrying obnoxious advertising. In other words, more than 99% of the newspapers and magazines in the United States carrying advertising are cooperating.

The next step in the campaign was directed to the druggists of the country. Out of the 48,500 appealed to, results up to the present, by return agreement card, show the cooperation of approximately 28,000, or nearly 60%.

After the druggists, the 131,780 legally recognized physicians in the United States were appealed to, with the result that agreement cards of cooperation have been received up to the present time, from approximately 60,000, or nearly 50%.

The campaign with the dental profession is just being launched; the campaign with the nursing profession and the training schools for nurses, is under way.

The campaign with the professional schools, hospitals, medical, dental, and pharmaceutical societies and associations,—national, interstate, state, county, and municipal,—has just been begun by a letter addressed to the deans of the medical and allied colleges of the country. That letter, with the two attachments which accompanied it, is inclosed herewith for your information.

For your cooperation in bringing to the attention of the medical and allied professions of the country this campaign inaugurated in the medical and allied colleges of the country, for the extension of teaching on this subject, and the better qualification of the physician, as a specialist in the treatment of venereal diseases, the United States Public Health Service respectfully requests that you publish the letter in your next issue; also, the "Report of a Conference with Medical Colleges Relative to Venereal Disease Control," and "Articles Relating to the New Status of Venereal Diseases in Medical Schools, etc.," which were attached to the letter.

Respectfully,

RUPERT BLUE,

Surgeon-General, U. S. Public Health Service.

Letter to Medical and Allied Colleges

SIR:—

The campaign for the control of venereal diseases in the United States by the Public Health Service makes it necessary for the medical, dental, and pharmaceutical schools, the hospitals, clinics, and the training schools for nurses, to cooperate to the utmost.

How may this be accomplished?

I. By calling a convocation of faculty, staff, and student body, at which:

(A) The dean will preside, state the object of the meeting, (viz., to indorse the propaganda undertaken by the U. S. Public Health Service, by direction, and under the authority, of Congress) and to appoint proper committees to put into effect the recommendations made by the chosen speakers, as to changes in curricula, etc.

(B) Selected speakers will deliver addresses on:

1. The sanitary attack upon the venereal diseases.
2. The better teaching of venereal diseases in schools, clinics, and hospitals.
3. The place of venereal diseases in our medical, dental, and pharmaceutical schools, in our hospitals, in our clinics, and in our training schools for nurses.
4. The importance of a proper knowledge of venereal diseases, not only to

physicians, but also to dentists, druggists, and nurses; further, to college physical directors.

II. By giving exhibitions to faculty, staff, students, and nurses, of the official Public Health Service educational six-reel photo-drama films:

(A) "Fit to Win" for men, which will be furnished free on application to your State Board of Health, or to this Bureau.

(B) "The End of the Road" for girls and women, which will be furnished free on application to the Boards of Health in the states of Connecticut, Illinois, Louisiana, and Virginia, or which may be had under pay arrangement from Mr. Isaac Silverman, Room 211, 1493 Broadway, New York City.

III. By arranging meetings to be addressed by:

(A) The president of the state board of health on the activities within the state, either by the state alone, or by the state in cooperation with the Public Health Service; the subjects explained being medical (the establishing of clinics), educational, legislative, social, law-enforcement.

(B) By the local, municipal, or county health office, who will detail the local activities on the same subjects.

(C) By the Public Health Service representative appointed to your state to work in cooperation with your state board of health, who will speak on the same activities, especially the establishment, organization, and general policy of the free clinics for the treatment of venereal diseases.

(D) By the U. S. Public Health Surgeons in charge of the clinics already established in your state, who will explain about location, staff, equipment, laboratory, treatment, records, etc.

IV. By complete, permanent Exhibits of official literature issued by:

(A) The U. S. Public Health Service:

1. Medical: reprints from U. S. Public Health Reports.

2. Educational: miscellaneous publications issued by the Division of Venereal Diseases.

Public Health Service literature will be furnished free for distribution to faculty, staff, student body, and nurses, on individual application to the Surgeon General, indicating list and quantity desired.

(B) State Boards of Health:

These publications are generally miscellaneous and may be had free on application to the State Board. Some states issue a weekly or monthly bulletin.

The campaign among the medical, dental, pharmaceutical schools, hospitals, and training schools for nurses having been recently launched in Washington, and all the universities, both white and colored, in the District of Columbia having already adopted the program, for your guidance in the plan outlined above there is inclosed herewith the report of the proceedings of the Georgetown University convocation, including the recommendations made by Dean George M. Kober of the Department of Medicine.

There is also inclosed herewith a list of articles which were published in the various leading dermatological and syphilogical journals of the United States within the last two years, upon the subjects mentioned above, to facilitate the short addresses.

A set of official literature consisting of (1) reprints from the "Public Health Reports," (weekly bulletin of the Public Health Service), and (2) miscellaneous publications issued by the Division of Venereal Diseases, is being mailed under separate cover.

In view of the foregoing exposition, what cooperation may the Public Health Service expect from your institution?

Your early reply with any suggestions you wish to make will be awaited with interest.

Respectfully,
RUPERT BLUE,
Surgeon General, U. S. Public Health Service.

Articles Relating to the New Status of Venereal Diseases in Medical Schools, Laboratories, Clinics, and Hospitals, Which Have Appeared in Dermatological, Syphilogical, etc., Journals Within the Last Two Years

Asst. Surgeon Gen. C. C. Pierce, U. S. Public Health Service.
"The Nation-Wide Control of Venereal Diseases."
Southern Medical Journal, Birmingham, Ala., March, 1919, 130

Asst. Surgeon Gen. C. C. Pierce, U. S. Public Health Service, and Major W. A. Sawyer, Medical Corps, U. S. Army.
"Venereal Disease Control in the Military Forces and Civilian Communities."
American Journal of Public Health, Boston, May, 1919.

Sir Wm. Osler.
"The Campaign Against Syphilis."
Lancet, London, 1917, i, 1787-1792.

A. S. Warthin.
"The New Pathology of Syphilis."
American Journal of Syphilis, St. Louis, 1918, ii, 425-452.

T. W. Murrell.
"Responsibility of the Physician to the Syphilitic and Through Him to the State."
Virginia Medical Monthly, Richmond, Va., 1918-19, xiv, 129-132.

Leredde and Rubinstein.
"Prophylaxe Medicale de la Syphilis; l'organization des Laboratories; necessite d'un Enseigement Technique."
Paris Med., 1917, XIX, 153-155.

J. H. Stokes.
"The In-Patient Hospital in the Control and Study of Syphilis."
New York, 1916, Social Hygiene, Baltimore, 1916, II, 207-231, Reprint.

L. W. Hamson.
"The Education of Students in Venereal Diseases."
Edinburgh Medical Journal, 1918, N.A.XXI, 138-145.

William Allen Pusey.
"The Sanitary Attack Upon Syphilis."
American Journal of Syphilis, St. Louis, Jan., 1917, 125.

H. H. Hazen.
"The Teaching of Syphilis."
American Journal of Syphilis, St. Louis, Jan., 1917, 135.

Charles J. White.
"The Place of Syphilis in our Medical Schools and Hospitals."
American Journal of Syphilis, St. Louis, Jan., 1917, 144.

Lewellys F. Barker.
"The Importance of a Knowledge of Syphilis, and Especially of Visceral Syphilis for General Medical Diagnosis."
American Journal of Syphilis, St. Louis, Jan., 1917, 149.

John A. Fordyce
"The Teaching of Syphilis."
The Journal of Cutaneous Diseases, Chicago, Nov., 1917, 717.

C. Morton Smith.
"The Teaching of Syphilis in School and Hospital."
The Journal of Cutaneous Diseases, Chicago, Nov., 1917, 726.

Walter James Heimann.
"The Teaching of Syphilis in Undergraduate Schools."
The Journal of Cutaneous Diseases, Nov., 1917, 732.

Symposium on "Teaching of Syphilis."

The Journal of Cutaneous Diseases, Chicago, Nov., 1917, p. 741.

DISCUSSION BY: Dr. H. H. Hazen, Washington, D. C., Dr. Harry G. Irvine, Minneapolis, Dr. A. Ravogli, Cincinnati, Ohio, Dr. Frank Edward Simpson, Chicago, Dr. Thomas W. Murrell, Richmond, Va., Dr. J. Frank Schamberg, Philadelphia, Dr. Harold N. Cole, Cleveland, Ohio, Dr. James Herbert Mitchell, Chicago, Dr. Isadore Rosen, New York City, Dr. Franklin W. Cregor, Indianapolis, Dr. John H. Stokes, Rochester, Minn., Dr. Boleslaw Lapowski, New York City, Dr. John A. Fordyce, New York City, Dr. C. Morton Smith, Boston, Mass., Dr. Walter J. Heimann, New York City.

Publications by the United States Public Health Service:

(1) "A Manual of Treatment of The Venereal Diseases," 1919.

(2) "Instructions to Medical Officers in Charge of State Control of Venereal Diseases, 1918." (Miscellaneous Pub. No. 19.)

Report of a Conference with Medical Colleges Relative to Venereal Disease Control

The first of a series of educational lectures and official film exhibitions for medical schools and members of the attending and nursing staffs of hospitals, which is part of the program of the Division of Venereal Diseases of the United States Public Health Service, was held on the evening of February 1, 1919, in the auditorium of the New National Museum, Washington, D. C., for the faculties and student bodies of the Medical and Dental Departments of Georgetown University.

A large, attentive and interested professional audience was assembled, and prior to the showing of the official film ''Fit to Win,'' the whole subject was introduced by Dean George M. Kober, of the School of Medicine, who said:

THE VENEREAL PROBLEM IN CIVIL LIFE

''We are here upon the invitation of Surgeon General Blue of the United States Public Health Service and by the courtesy of the authorities of the Smithsonian Institution to discuss the most important health problem of the twentieth century.

''We have indeed reason to be proud of the progress and achievements of hygiene when we recall the fact that the average span of human life has been lengthened in civilized communities from eighteen years in the sixteenth century to nearly fifty years at the present time, and that the span of life in our own great country since 1880 has been lengthened fully eight years. In 1880, 326 out of 100,000 of population in the United States perished every year from tuberculosis; in 1916 the rate had fallen to 141.6 per 100,000. Had the former rate continued, there would have been 322,027 deaths instead of 143,000, a saving of 179,027 in one year alone. The decrease in typhoid fever, diarrhoeal diseases, malaria, and other diseases amounts in many instances to over 50 per cent. Among the most important factors which have brought about this gratifying result is the improvement of the air we breathe, the water we drink, higher standards of living, the crusade against insect, water, and milk-borne diseases, and attention to personal hygiene.

''In spite of these achievements sanitarians observed that certain diseases, notably diseases of the heart, blood vessels, and kidneys; apoplexy, insanity, cancer, and last but not least the so-called vice diseases, with all their evil and far-reaching consequences, were apparently on the increase. This matter appeared to me of such grave importance that as chairman of the Committee on Social Betterment of President Roosevelt's Homes Commission I devoted in 1908 special attention to the study of the venereal peril, and we learned that out of 274,611 patients treated in the city hospitals of Washington there were no less than 27,947 cases of venereal diseases, and hence very properly urged a crusade against the 'social evil' by educational and State methods. The publication of the report naturally aroused more or less interest and also some opposition.

''In 1909 the American Public Health Association, appreciating the gravity of the situation, appointed a committee to consider and report upon the best method of educating the public with respect to the communicability and prevention of gonorrhea and syphilis.

''Our committee had no accurate statistical data as to the prevalence of these diseases in civil life apart from the statistics collected for the President's Homes Commission. We knew in a general way that fully 80 per cent of all the operations for inflammatory diseases peculiar to women are of gonorrheal origin;

that the same germ was responsible for the blindness in 15,000 of the 50,000 blind persons in the United States; that Dr. Cole, in Osler's Modern Medicine, cited 19 epidemics of gonorrhea, with 660 cases among children in various hospitals; that Dr. Holt had observed 273 cases of gonorrhea in the 'Babies' Hospitals in New York, and that Neisser, the discoverer of the germ, estimates that more than 45 per cent of all involuntary childless marriages are due to this cause.

"We also knew that syphilis was responsible for 42 per cent of abortions and miscarriages, and that from 60 to 86 per cent of the offspring of syphilitics die before, or shortly after birth, and those who survive are subject to physical and mental defects; that it was the cause in over 90 per cent of the cases of locomotor ataxia, and a prolific cause of apoplexy, paralysis, softening of the brain, insanity, diseases of the heart, blood vessels, and other vital organs.

"But when we cast about for exact facts as to the prevalence of these diseases we had to fall back upon a study of the statistics of the Armies and Navies of the world, collected by Assistant Surgeon General J. R. Kean of the Army, and Surgeon Fiske of the Navy, which show the total admission rates for venereal diseases per 1,000 of mean strength as follows:

	Year	Syphilis	Chancroid	Gonorrhea	Total Venereal
United States Army	1908	30.45	30.77	135.77	196.99
United States Navy	1909	26.49	28.23	105.11	159.8
Japanese Navy	1907	.....	.....	......	139.8
British Navy	1908	37.46	17.87	67.16	122.5
British Army	1908	35.1	28.23	40.7	104.0
Spanish Army	1907	11.6	27.84	28.4	67.8
German Navy	1908	17.3	9.5	36.4	63.2
Russian Army	1907	17.7	12.2	30.2	60.1
Austrian Army	1907	16.0	10.1	28.1	54.2
Japanese Army	1907	10.1	10.4	17.1	37.6
Belgian Army	1907	6.2	.....	19.99	26.2
Dutch Army	1905	4.6	.....	17.0	21.6
Prussian Army	1907	4.4	2.1	12.2	18.7
Bavarian Army	1907	3.3	0.97	10.9	15.2

"These figures brought out the lamentable fact that the United States and Great Britain led all the other armies and navies in the prevalence of venereal diseases. We do not believe that our population is less virtuous, but are inclined to the opinion that this undue prevalence is largely, if not entirely, due to the fact that the sentiment in these two countries is strongly against recognizing the evil, and therefore had not been made a subject of popular education. As the result of ignorance and neglect, the admission rate for this class of diseases in the United States Army had been steadily increasing, and was more than ten times greater than in countries where serious attention has been paid to the consideration of the problem.

"It may be contended that enlisted men of the Army and Navy are not representative of our civil population, but let us not forget that, after all, they were 'picked men,' free from disease upon admission, and that they do not contract these diseases in their own quarters, but in surrounding civil communities, just as they would contract typhoid fever or any other communicable disease if prevalent in the respective locality.

''We believe, therefore, that our Army and Navy statistics furnish a fairly accurate index of the relative frequency of sexual diseases among the celibate male population in this country.

''Indeed, the committee concluded that venereal disease may be even more prevalent in civil life than in the Army and Navy, and until demonstrated to the contrary it could not be considered unfair to assume that every year one youth out of every six in this country, between the ages of 17 and 24, contracts a venereal infection.

''This belief, enunciated ten years ago, was not generally accepted by the profession and the public.

''The present war, however, fully confirmed our conclusions, and revealed the fact that the total admission rate for venereal diseases per 1,000 men in five National Army camps, viz., Dix, Lee, Upton, Meade, and Pike, was 337.2.

''Of the 45,000 cases reported between March 29 and November 15, 1918, nearly 96 per cent had contracted the disease before enlistment. These and subsequent findings no longer left any doubt as to the seriousness of the problem in civil life. It has been estimated that over 280,000 cases have been treated in the United States Army, and that five out of every six of these cases came into the Army afflicted with venereal disease. It has been conclusively demonstrated that these diseases constituted the greatest single cause of disability in the Army and that five-sixths of this burden was brought into the Army from all ranks of society in civil life. I hope these figures will convince you that these diseases constitute a most serious menace to the health and vigor of our entire population.

''It is a great satisfaction to know that the Congress has authorized the United States Public Health Service to deal with the problem in an adequate manner. We are fortunate to have with us this evening Assistant Surgeon General C. C. Pierce, who will enlighten us as to the methods adopted by the Public Health Service to stamp out this greatest scourge of mankind.

''Personally, I confidently expect the greatest possible beneficial results from the campaign inaugurated by the Public Health Service, and, although it may seem to many a disagreeable subject for public education, remember always that ignorance is not innocence and is oftentimes the surest road to guilt. I take great pleasure in presenting Dr. Pierce.''

Assistant Surgeon General C. C. Pierce, in charge of the Division of Venereal Diseases, United States Public Health Service, who followed, explained at length the Government's program. He said:

'' 'The passage of the Chamberlain-Kahn bill, creating the Interdepartmental Social Hygiene Board, and the Division of Venereal Diseases in the United States Public Health Service, was one of the most important pieces of public-health legislation in recent years,' said Surgeon General Rupert Blue of the United States Public Health Service recently.

''This action on the part of the Congress has enabled the constituted authorities of our Government to carry on a cooperative program for the control of venereal infections throughout the United States. Prior to the passage of this Act the United States Public Health Service, realizing the urgent necessity for control measures for venereal diseases, had opened negotiations with the various State Boards of Health, with a view of having established in each State a bureau of venereal diseases, to have general supervision over all phases of this important work. The plan was to have an officer of the Public Health Service stationed in each of the various States, for the purpose of cooperating with the State Board of Health in establishing a fourfold work, as follows:

"(a) Securing the reporting of venereal infections, in accordance with the State laws or State Board of Health regulations.

"(b) Carrying on repressive measures, including the isolation and treatment in detention hospitals of infected persons who are unable or unwilling to take the necessary measures to prevent themselves from becoming a menace to others.

"(c) Establishment of free clinics for the treatment of venereal diseases, and extending the facilities for early diagnosis and treatment by providing proper laboratories to make exact diagnoses and examinations to determine when patients might be released as noninfectious.

"(d) To carry on a general educational campaign to inform the public, as well as the infected individuals, regarding the nature of these diseases and the manner in which they are spread.

"In attacking venereal diseases as a public-health problem the work is designed to be carried on as near as possible as it would be for any other communicable diseases. It is known to the medical profession that these diseases are spread by certain causative organisms passing from an infected individual to a well person. When the cause of the disease is known, and its method of spread can be recognized, the precautions to be taken to prevent spread may be developed.

"One reason that venereal diseases have not received the attention from health officers in the past which their seriousness warrants was the many complicated factors which enter into the conditions favoring the spread of these infections. In the case of smallpox or malarial fever there is no shame or moral stigma attached to the acquirement of these diseases. However, in the case of syphilis and gonorrhea, which spread very largely through illegitimate practices, there is usually a certain amount of moral stigma attached to the acquirement. However, as was recently well said by Madam Avril de St. Croix, 'There is no shame attached to the disease itself,' and if health officers will avoid the complications of social, moral, and economic factors, the actual control of those already infected can be successfully carried out.

"It is impossible to attempt to prevent the further spread of venereal infections unless a systematic campaign for the control of carriers takes place. The vast majority of the venereal infections are acquired from prostitutes (the word being used to mean anyone who indulges in promiscuous sexual relations). These carriers should be controlled just as the carriers of typhoid fever, diphtheria, and meningitis. Therefore, the elimination of prostitution is one of the phases of this important public-health work.

''The magnitude of the problem need not deter one from an energetic effort to accomplish the desired result. Just because prostitution as a business enterprise has existed from the times of remote antiquity is no reason why it should continue to exist throughout the future. Bubonic plague has existed for centuries, and yet it would be a ridiculous procedure to ignore the known fact that plague is spread by infected fleas from diseased rats. Plague has lost its terrors for all civilized communities because its methods of spread and the means for its control are well known. Prostitution forms the great reservoir from which the venereal infections spread, and it is therefore incumbent upon all interested in the control of venereal diseases to energetically attack prostitution.

''Surgeon General Blue said in a communication a few months ago: 'The Public Health Service intends to fight prostitution to a finish.' This does not mean that the sporadic effort, following an intensive campaign for civic righteousness whereby the red-light district of the town is closed by official order, is to be the extent of the work. Reconstructive measures adapted to reclaim and return to society the unfortunate women engaged in this ancient and dishonorable calling must necessarily be a part of the program. The large feeble-minded class must receive custodial care. To clean up the sinks of iniquity in our various urban communities is a process exactly analogous to the draining of the swamps to prevent the spread of malaria; or the abolishing of rain-water barrels and cisterns to prevent the spread of yellow fever. In fact, it is a more logical and direct procedure to eliminate the foci from which venereal diseases spread than it is to abolish the breeding places of carriers of malaria and yellow fever.

''There are no intermediate carriers of the venereal infections—syphilis and gonorrhea spreading only by direct personal contact.

''Another phase of the work which has advanced progress is the teaching of continence. No one would advise or permit a patient to kiss a diphtheria carrier and then take a prophylactic dose of diphtheria antitoxin as a preventive measure. The best advice to give is to keep away from the diphtheria carrier. This applies also in the case of venereal diseases. Why should one expose himself to the infection and then depend upon prophylactic measures to prevent the development of the disease? This is not meant as an argument against the early prophylactic treatment; such a measure has a very definite usefulness, but is of secondary importance to the logical procedure of avoiding exposure to infection.

''In order to achieve success in the control of venereal infections, the fourfold plan mentioned earlier must be carried out; *i. e.*, to treat those infected, enforce the laws designed to prevent the spread of these infections, eliminate foci of infection, and educate the general public.

''It is gratifying to be able to say that forty-four of the States are now carrying on this standard program for venereal-disease control. While many persons have heartily entered into this work on account of the patriotic appeal made to them that it was a necessary war measure, they should now realize that it is just as necessary in time of peace. The great problems of reconstruction can not be handled by our people unless the entire citizenship of the country is maintained at the highest standard of efficiency. The prevalence of venereal infections throughout the whole fabric of civilization is so enormous that there are no other causes that produce such widespread misery, suffering, loss of efficiency, and damage to posterity as the venereal diseases. Therefore, now that the world has been made safe for democrary, let us likewise make it safe for posterity.''

The activities, present and contemplated, of the Department of Health of the District of Columbia were set forth in an address by Dr. Wm. C. Fowler, Health Officer, who said:

''Ladies and Gentlemen: I am going to endeavor to explain to you the program of the local health department in its efforts to suppress this social evil.

''The Health Department of the District of Columbia is earnestly cooperating with the United States Public Health Service in this campaign.

''The Public Health Service has furnished us with a number of pamphlets issued by them relating to these diseases, and our Department has distributed them very freely among those people of the District through whom we believe the most good can be accomplished. We have sent these pamphlets to the officers of fraternal organizations, the presidents of all the citizens' associations, and have distributed them through other channels, and I might say to you here that there has been a very generous response from the people. Many of them have indicated their willingness to do all in their power to assist in this campaign, and many of them have called for additional copies of pamphlets for distribution.

''The Health Department has also had printed and posted in many of the public places throughout the District placards relating to venereal diseases and announcing that it has established and is maintaining at No. 409 15th street N. W., a clinic for the treatment of such diseases. This clinic is maintained entirely by a small appropriation from Congress to the Health Department. It is, I feel perfectly safe in saying, one of the best-equipped clinics of its kind. It has only recently been started, but the number of patients applying is rapidly increasing. The department at the present time has two physicians in attendance. These two physicians are men recognized as specialists in their particular line of work. This week a nurse was employed in connection with the work. Our plan is to use this nurse, when not busy in the clinic, to visit the homes and follow up persons who apply for treatment. In other words, if we can get them to the clinic, it is our purpose to follow up each patient and see that they continue to return for treatment until they have recovered from their trouble. We also intend to prevent infected persons spreading the diseases to others, so far as may be possible. As this clinic grows, we expect to add to our staff.

''The Health Department of the District of Columbia is ready and anxious to cooperate in every way in this campaign. A circular has been sent to all the physicians in the District, notifying them that the Health Department Laboratory facilities are at their disposal. The laboratory will make examinations of blood without cost; it will make examinations of other specimens submitted without cost. I hope the medical profession of this city will accept this offer and avail themselves of all the facilities we have. It is only through the united efforts of all concerned that we can accomplish what we are trying to do.''

Before the film was presented by Assistant Surgeon General C. C. Pierce, Dr. George M. Kober, as Dean of the Medical Department of Georgetown University, made the following recommendations:

''Ladies and Gentlemen: Before turning over the meeting to Dr. Pierce, for the demonstration of the film, I think it is only fair to express our deep appreciation to Surgeon General Blue for arranging this meeting and to Dr. Pierce for his able and instructive address. We also owe thanks to Dr. Fowler, our efficient Health Officer, for his presence and remarks.

''I also wish to impress upon the medical students and teachers, as well as the members of the hospital and nursing staffs of Georgetown University, their duties and responsibilities in this great campaign against the venereal evil. In the light of our knowledge of the occurrence of epidemics of gonorrhea in children's and babies' hospitals, even the nurses should be interested in this movement, not only as a matter of self-protection, but also to prevent the spread among innocent victims.

''I consider it clearly the duty of every medical student to become perfectly familiar with the etiology, treatment, and prevention of these important diseases.

''I consider it clearly the duty of every professor connected with the medical school, who refers in his lectures to the evil and far-reaching consequences of venereal diseases, to lose no opportunity to point out the importance of prevention of these diseases by educational and State methods.

''This obligation should be especially emphasized by the professor of hygiene.

''I consider it also the duty of every physician to take a deep interest in the educational campaign, because it is not only a moral and medical, but also a social and economic problem that involves the very future of our nation.

''I consider it to be clearly our duty to assist in the formation of social hygiene associations, with lectures emphasizing Christian chastity, and how sexual purity may be attained.

''We should also be instrumental in the organization of dispensaries and hospitals for the treatment of such diseases, especially for such persons as are unable to pay.

''I consider it clearly the duty of every physician to support the enactment and enforcement of laws compelling the reporting of cases of venereal infections.

''In order to stamp out the sources of contagion it is necessary to locate the sources of infection, and this can only be done by compulsory reports. It is not necessary to know the name; indeed, we should spare the feelings of the patient, because, after all, he is more to be pitied than to be blamed.

''These reports can be made by number, and so long as the patient remains faithful in undergoing treatment there is no reason why his name should be revealed; but if he neglects to remain under treatment until he is well, he should be reported by name, so that he may be compelled to undergo treatment until he is fit to mingle with the public. The community is entitled to this protection, because these diseases are communicable in an extra-genital way, particularly in the dentist's chair and barber shop.

''In the interest of a strong and vigorous nation it is clearly our duty to advocate a law compelling certificates of clean health before licenses for marriage are issued, so that the sins of the parents may not be visited upon future generations. It should be borne in mind that the eradication of communicable diseases is the highest aim of scientific medicine, and in this effort the loyal cooperation of the physician, patient, and the public is of the utmost importance.''

At the conclusion of Dr. Kober's remarks and before the exhibition of the film, Dr. Charles V. Herdliska, Assistant Educational Director of the Division of Venereal Diseases, explained the literature being used in the nation-wide campaign for the control of venereal diseases. He said:

''The official literature of the United States Public Health Service in this propaganda against venereal diseases consists of two kinds: One kind consists of reprints by the Government Printing Office of articles which first appeared in the 'Public Health Reports,' issued weekly by the United States Public Health Service. The second kind consists of miscellaneous publications issued by the Division of Venereal Diseases of the Public Health Service. The reprints from the 'Public Health Reports' are mostly scientific in character, whereas the miscellaneous publications are for every phase and walk of life. There is literature for the industrial plant and the commercial institution; for railroads and shipping; for the church; for the club; for the community center; for the home; for the libraries and the schools; for the high schools; for the colleges, and the universities.

''The Public Health Service has placed an exhibit of Public Health reprints on one of the bulletin boards, and an exhibit of miscellaneous pamphlets on the other, for your inspection after the meeting. Copies of the reprints may be had from the Government Printing Office; the miscellaneous prints may be had free on application to the Surgeon General of the United States Public Health Service. For this particular meeting tonight, in which the medical and dental schools and professions and the hospital staffs and training schools for nurses are interested, the Public Health Service has prepared a selected set. This set is contained in envelopes, one of which may be obtained by each of you at the door as you leave the hall.

''The war has brought the great American awakening. In the prosecution of this propaganda, authorized and directed by Congress, the United States Public Health Service not only solicits, but feels assured of your sympathetic interest and enthusiastic cooperation.''

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Original Articles

STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. V

THE PRESERVATION OF COMPLEMENT SERUM

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SINCE the complements of individual guinea pigs tend to vary in fixability and a mixture of complements having proved more reliable for the Wassermann reaction than single complements,[1] a satisfactory and practical method for the preservation of complement becomes a matter of considerable economic importance and particularly in laboratories conducting a small number of tests at one time and too few to require all the mixed complement serum from two or more exsanguinated pigs.

Probably the best method for securing a mixture of complements without undue waste and expense consists in keeping on hand a stock of large healthy animals and bleeding them in rotation from the heart or external jugular vein as complement is required; for various reasons however this method may not be practical for certain laboratories, whereas a reliable method of preserving complement may enable the serologist to exsanguinate at least two or three animals and utilize the mixed complements without waste over a certain period of time.

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*Investigation aided by funds accruing from the dispensing of arsphenamine.

SCOPE OF INVESTIGATION

Probably the oldest method for the preservation of complement is that by freezing as mentioned by Morgenroth[2] who states that serum kept at –10 to –15° C. preserves the various constituents for a long time; Penecke[3] has also stated that complement may be preserved by this means for four to five weeks. Weston[4] reports that serum kept at –15° C. showed no appreciable deterioration in hemolytic activity after a period of three months and one of three specimens was preserved for five months. Stern[5] has preserved complement in this manner, but has stated that deterioration in fixability by mixtures of syphilitic serum and organic extracts develops prior to changes in hemolytic activity. More recently Moledesky[6] has advocated the preservation of complement serum frozen solid in test tubes packed in a mixture of ice and salt in a thermos bottle and states that the serum keeps indefinitely under these conditions.

For several years various salts have been used for the preservation of complement serum and particularly sodium chloride in from 8 to 37 per cent; one of us (J. A. K.) has used 17 per cent sodium chloride (0.17 grams to each cubic centimeter of serum) with considerable success when the serum was kept at a low temperature. By diluting each cubic centimeter of serum with 19 c.c. distilled water a 1:20 dilution in isotonic salt solution was obtained. Austin,[7] Thompson,[8] Ottenberg,[9] and Neill[10] have used sodium chloride with success; the technic employed by Austin, Thompson, and Neill will be described later.

Grigorowitsch[11] and Silber[12] have added 5 per cent magnesium sulphate to serum followed by drying and apparently with successful results; Noguchi[13] has dried guinea pig complement in paper as a means of preservation and to simplify the use of this constituent in his test, but found that deterioration occurred rather rapidly.

Rhamy[14] has advocated the preservation of complement with sodium acetate and Ruediger[15] has employed glycerin; detailed descriptions of their methods will be given later in a description of technic employed in our experiments.

During the past three years we have conducted a large number of experiments with guinea pig and human complements preserved with these different methods and the results are summarized in this paper; in each experiment the preserved complement was tested fresh and and at varying intervals for the following three values:

1. For hemolytic activity in an antisheep system.
2. For fixability in mixtures of syphilitic sera and various organ extracts (antigens).
3. For susceptibility to nonspecific fixation by serum and organ extracts alone, better known as the anticomplementary effects shown by the serum and the extract or antigen.

In the majority of published accounts of such experiments it would appear that hemolytic activity alone was accepted as the criterion of the quality of the preserved serum, whereas in our experiments we have found that a slight decrease in specific fixability alone or associated with an increased susceptibility to nonspecific fixation are the earliest changes of deterioration and that hemolytic activity may be preserved for longer periods in an otherwise unsatisfactory serum.

GENERAL TECHNIC

Some of our experiments were conducted with the complements of individual persons and guinea pigs but in the majority of experiments mixtures of the complements of six or more persons and two or more guinea pigs were employed. In all instances the complements were tested fresh and at varying periods after the addition of preservative, being kept in a refrigerator at 4° to 9° C. in the intervals.

For determining the hemolytic activity of preserved complements the same antisheep hemolysin was employed in the same dose throughout each experiment and as titrated at intervals with fresh complements showed no appreciable deterioration over a period of four to five weeks which was the longest period of any single experiment. Washed sheep cells were used in dose of 1.0 c.c. of a 2½ per cent suspension or 0.1 c.c. of a 5 per cent suspension; inasmuch as the hemolytic activity of a complement serum varies according to the doses of hemolysin and cells employed and the duration of incubation, the figures given in the tables summarizing our experiments are, of course, not absolute, but by keeping the hemolysin and the technic as constant as possible throughout each experiment the rate of deterioration of each serum is shown as accurately as we could determine. In all experiments the results of the complement titrations were read after one hour of incubation in a water-bath at 38° C.

For determining the fixability of preserved complements by syphilitic serum and extract, the same extracts were employed throughout each experiment with no appreciable change in antigenic sensitiveness or increased anticomplementary activity; in some experiments the same syphilitic serum was employed throughout, being preserved in a frozen condition. In other experiments different syphilitic sera were used during the course of the experiments, the fixability of the preserved complement being compared with that of fresh complement. In conducting the tests for fixability three methods were employed, namely, the usual method of using the complement in a fixed dose of two units with constant doses of syphilitic serum and organ extracts and expressing the results as +, + +, + + +, + + + + and – ; second, a method consisting in using the complement in an increasing number of units with constant doses of syphilitic serum and extract after the method of Browning and McKenzie; and third, using the syphilitic serum in decreasing doses with a constant dose of antigen and two units of complement.

Primary incubation was of one hour in a water-bath at 38° C., when two units of hemolysin and the indicator antigen were added followed by incubation for one hour in a water-bath.

Susceptibility to nonspecific fixation or the so-called anticomplementary activity of serum and antigen alone and which we have found particularly important in this work, was determined in the serum and extract controls of each test as conducted by the usual method and was brought out in a particularly definite and clear manner by the method of Browning and McKenzie, whereby the anticomplementary effects of serum and extract alone are measured directly according to the number of units of complement absorbed or fixed by each.

METHODS OF PRESERVATION

In our experiments complement sera were preserved after various methods as follows:

1. *By Refrigeration.*—Undiluted sera and sera diluted 1:10 with physiologic saline solution were kept in bulk in test tubes packed in mixtures of ice and salt and kept in a refrigerator. As a general rule the serum was quickly frozen solid, but thawing was permitted to occur at intervals at room temperature in order to secure serum for titrations and this may have aided in the deterioration of the serum.

In other experiments undiluted and diluted sera were kept in an ordinary refrigerator at a temperature varying from 4° C. during the night to 9° C. during the day.

2. *With 17 per cent Sodium Chloride.*—To each cubic centimeter of serum was added 0.17 gram pure sodium chloride and the serum kept at 4° to 9° C. By diluting 1 c.c. of serum with 19 c.c. distilled water a 1:20 dilution of complement was obtained in isotonic solution.

3. *With 8.5 per cent Sodium Chloride.*—In each 10 c.c. of serum was dissolved 0.85 gram of pure sodium chloride and the mixture kept at 4° to 9° C.; when required, 1 c.c. of this serum was diluted with 9 c.c. of distilled water yielding a 1:10 dilution of complement in isotonic solution.

4. *With 4.3 per cent Sodium Chloride.*—In each 10 c.c. of serum was dissolved 0.43 gram of pure sodium chloride and the mixture kept at 4° to 9° C.; when required, 1 c.c. of this serum was diluted with 4 c.c. of distilled water, yielding a 1:5 dilution of complement in isotonic solution.

5. *With Sodium Chloride after the Method of Thompson.*—An 8.1 per cent solution of pure sodium chloride in distilled water was prepared and autoclaved; equal parts of complement serum and this salt solution were mixed and kept at 4° to 9° C. When required, 1 c.c. of this mixture was diluted with 4 c.c. of distilled water, giving a 1:10 dilution of complement in isotonic solution.

6. *With Sodium Chloride after the Method of Austin.*—A 25 per cent solution of pure sodium chloride in distilled water was prepared and sterilized; to one part of complement serum was added 1½ parts of this salt solution and the mixture kept at 4° to 9° C. When required, we diluted 1 c.c. of the mixture with 3 c.c. of 0.5 per cent sodium chloride solution, which gave a 1:10 dilution of complement in isotonic solution.

7. *With Sodium Chloride after the Method of Neill.*—A saturated solution (36 per cent) of pure sodium chloride was prepared in hot distilled water, cooled, filtered, and sterilized; to each 1 c.c. of com-

plement serum was added 0.1 c.c. of this salt solution and the mixture kept in a refrigerator at 4° to 9° C. When required, 1 c.c. of the preserved complement was diluted with 3 c.c. of distilled water which restored the normal tonicity, and further diluted with 6 c.c. of 0.85 per cent sodium chloride solution yielding a 1:10 dilution of complement.

8. *With Sodium Acetate after the Method of Rhamy.*—A 10 per cent solution of pure sodium acetate in 0.9 per cent solution of sodium chloride was prepared and sterilized; to one part of complement serum was added 1½ parts of acetate solution and the mixture kept at 4° to 9° C. When required, 1 c.c. of this mixture was diluted with 3 c.c. of 0.85 per cent sodium chloride solution yielding a 1:10 dilution of complement.

9. *With 4.3 per cent Magnesium Sulphate.*—In each ten cubic centimeters of serum was dissolved 0.43 gram pure magnesium sulphate and the mixture kept at 4° to 9° C.; when required 1 c.c. of this preserved serum was diluted with 4 c.c. of 0.85 per cent sodium chloride solution, yielding a 1:5 dilution of complement.

10. *With Glycerol after the Method of Ruediger.*—To each 3 c.c. of complement serum was added 1 c.c. of Merck's blue label glycerol after sterilization and the mixture kept at 4° to 9° C. When required, 1 c.c. of this mixture was diluted with 7.5 c.c. of 0.85 per cent sodium chloride solution, which gave a 1:10 dilution of complement.

11. *Dried in Filter Paper after the Method of Noguchi.*—The special filter paper Schleicher and Schull No. 597 was cut into squares 100 x 100 mm. and evenly saturated with measured amounts of complement serum, rapidly dried by fanning with cold air, cut into strips 5 mm. in width and preserved at 4° to 9° C. in tightly stoppered test tubes.

12. *Dried and Pulverized.*—Measured amounts of complement serum were rapidly dried by fanning with cold air upon weighed evaporating dishes followed by weighing and calculation of weight of dried serum per cubic centimeter of fluid serum; each cubic centimeter of fluid serum yielded about 0.132 gram of dried product. The dried serum was kept at 4° to 9° C. in tightly stoppered tubes and when required 0.132 gram was dissolved in 10 c.c. of physiologic salt solution, giving a 1:10 dilution of dried serum, equivalent approximately to 1:10 dilution of fluid serum.

13. *Dried and Pulverized after the Addition of 1 per cent Sodium Chloride.*—To each 10 c.c. of complement serum was added 0.1 gram of pure sodium chloride followed by rapid drying on weighed evaporating dishes and calculation of the weight of dried product in proportion to each cubic centimeter of serum as required.

14. *Dried and Pulverized after the Addition of 5 per cent Magnesium Sulphate.*—To each 10 c.c. of complement serum was added 0.5 gram of pure magnesium sulphate followed by rapid drying on weighed evaporating dishes and calculation of weight of dried product in proportion to each cubic centimeter of serum.

RESULTS

The Preservation of Diluted Complement Kept at 4° to 9° C.—The qualities of guinea pig complement diluted 1:10 with physiologic salt solution and kept in a refrigerator at 4° to 9° C. are shown in Tables I and II.

TABLE I

THE HEMOLYTIC ACTIVITY OF GUINEA PIG COMPLEMENT DILUTED 1:10, PRESERVED IN A REFRIGERATOR AT 4° TO 9° C.

COMPLEMENTS	UNIT OF COMPLEMENT*							
	FRESH	1 day	2 days	3 days	5 days	7 days	14 days	21 days
1	0.2	0.2	0.3	0.4	0.6	1.4	2.0	4.0
2	0.1	0.2	0.3	0	0	0.8	1.5	2.5
3	0.2	0.2	0.4	0.5	0.8	3.0	0	0
4	0.2	0.3	0.3	0.5	0.8	1.8	2.4	0

*Titrated in an antisheep system.

TABLE II

THE FIXABILITY OF GUINEA PIG COMPLEMENT DILUTED 1:10 PRESERVED IN A REFRIGERATOR 4° TO 9° C.

AGE OF COMPLEMENT	RESULTS OF WASSERMANN TESTS							
	0.1	0.01	0.001	0.0001	0.00001	Serum Control	Antigen Control	Hemolytic Control
Fresh	++++	++++	+	±	—	—	—	—
1 day	++++	++++	+	+	—	—	—	—
2 days	++++	++++	++	+	—	—	—	—
3 days	++++	++++	+++	++	+	±	—	—
5 days	++++	++++	+++	+++	++	++	+	—
7 days	++++	++++	++++	++++	+++	+++	+++	—

Hemolytic activity usually remained unchanged for twenty-four hours followed by gradual deterioration, until at the end of the first week, the hemolytic unit was from 7 to 9 times greater than the unit of fresh serum; after this time deterioration was quite rapid as shown graphically in Chart 1.

As studied over a period of a week, fixability remained unchanged, but an increased susceptibility to nonspecific fixation was sometimes apparent as early as the third day, and practically always by the end of the first week, rendering the complement unduly sensitive and unfit for diagnostic tests.

As a general rule it may be stated that diluted complement kept in an ordinary ice refrigerator with fluctuations in temperature can not be relied upon after three days, following collection of the serum.

The Preservation of Diluted Complement Repeatedly Frozen and Thawed.—Complement diluted 1:10 and frozen solid in mixtures of ice and salt was found to keep for longer periods of time. The hemolytic activity remains quite constant for two or three days, but by the end of the week the unit is likely to be at least three times greater than the unit of fresh serum. It should be remembered in this connection that in our experiments the serum was frozen in bulk and permitted to thaw at room temperature at frequent intervals so that the results represent the keeping qualities of serum repeatedly frozen and thawed. After the first week deterioration was more rapid. (Table III and Chart 1.)

TABLE III

THE HEMOLYTIC ACTIVITY OF GUINEA PIG COMPLEMENT DILUTED 1:10, FROZEN SOLID

COMPLEMENTS	UNIT OF COMPLEMENT								
	Fresh	1 day	2 days	3 days	4 days	5 days	7 days	14 days	21 days
1	0.2	0.2	0.2	0.3	0.5	0.8	1.2	2.0	3.0
2	0.1	0.1	0.2	0.2	0.3	0.3	0.5	1.0	1.8
3	0.2	0	0.2	0	0	0.6	0.8	2.5	3.0
4	0.2	0.2	0.2	0.4	0.5	1.0	1.8	2.0	2.8

Fixability remained unchanged for at least five days; at the end of seven days a slight decrease in fixability and increased susceptibility to the anticomplementary influences of serum alone and antigen alone became apparent.

Under the conditions in which our tests were conducted it may be stated that guinea pig complement diluted 1:10 may be kept for at least five days when frozen solid.

TABLE IV

THE FIXABILITY OF GUINEA PIG COMPLEMENT DILUTED 1:10 PRESERVED IN A REFRIGERATOR AT 4° TO 9° C.

AGE OF COMPLEMENT	RESULTS OF WASSERMANN TESTS							
	0.1	0.01	0.001	0.0001	0.00001	Serum Control	Antigen Control	Hemolytic Control
Fresh	++++	++++	+	±	—	—	—	—
1 day	++++	++++	+	±	—	—	—	—
2 days	++++	++++	+	±	—	—	—	—
3 days	++++	++++	+	+	—	—	—	—
4 days	++++	++++	++	+	—	—	—	—
5 days	++++	++++	+++	++	—	—	—	—
7 days	++++	++++	+++	+++	++	+	+	—
14 days	++++	++++	+++	+++	+++	++	++	—
21 days	++++	++++	+++	+++	+++	+++	+++	—

The Preservation of Undiluted Complement Kept at 4° to 9° C.—Undiluted complement does not deteriorate as rapidly as diluted serum. When kept in an ordinary refrigerator at 4° to 9° C. the unit of hemolytic activity at the end of seven days was from two to three times greater than the unit of fresh serum; at the end of two weeks the unit was from five to nine times greater than the unit of the serum when fresh and after three weeks from ten to twenty times higher. (Table V, Chart 1.)

TABLE V

THE HEMOLYTIC ACTIVITY OF UNDILUTED GUINEA PIG COMPLEMENT, PRESERVED AT 4° TO 9° C.

COMPLEMENTS	UNIT OF COMPLEMENT IN C.C. UNDILUTED SERUM					
	Fresh	1 day	2 days	7 days	14 days	21 days
No. 1	0.035	0.04	0.05	0.06	0.2	0.4
No. 2	0.03	0.03	0.06	0.08	0.16	0.6
No. 3	0.02	0.02	0.04	0.06	0.18	0.3

The fixability of complement kept under these conditions remained practically unchanged for about seven to ten days; usually by the end of the second week and always by the third week the serum had become highly sensitive to nonspecific fixation and unfit for further use (Table VI).

TABLE VI

THE FIXABILITY OF UNDILUTED GUINEA PIG COMPLEMENTS, PRESERVED AT 4° TO 9° C.

PRESERVATION	PIG 1		PIG 2		PIG 3	
	Wassermann	Control	Wassermann	Control	Wassermann	Control
Fresh	++++	—	++++	—	++++	—
1 day	++++	—	++++	—	++++	—
2 days	++++	—	++++	—	++++	—
7 days	++++	—	++++	—	++++	+
14 days	++++	—	++++	+	++++	++
21 days	++++	++	++++	++	++++	++++

The Preservation of Undiluted Complement Repeatedly Frozen and Thawed.—Undiluted guinea pig and human complements frozen in bulk in test tubes in mixtures of ice and salt, were easily kept for at least two weeks; in our experiments thawing of the sera was permitted at room temperature at frequent intervals so that the results express the keeping qualities of complements alternately frozen and thawed. At the end of the first week the unit of hemolytic activity was about double that of the same serum when fresh; at the end of the second week the unit was five to six times higher and at the end of the third week from ten to fifteen times higher than the unit of fresh serum (Table VII, Chart 1).

TABLE VII

THE HEMOLYTIC ACTIVITY OF UNDILUTED GUINEA PIG AND HUMAN COMPLEMENTS, REPEATEDLY FROZEN AND THAWED

COMPLEMENTS	Fresh	1 day	2 days	3 days	5 days	7 days	9 days	14 days	21 days
Guinea pig*	0.03	0	0.03	0	0.05	0.06	0.1	0.15	0.2
Guinea pig**	0.02	0	0.015	0	0.05	0.06	0.08	0.1	0.2
Guinea pig**	0.035	0.035	0.03	0.05	0.08	0.1	0.02	0.3	0.2
Guinea pig**	0.02	0.02	0.025	0.025	0.05	0.08	0.08	0.15	0.4
Guinea pig**	0.02	0.02	0.02	0.06	0.06	0.08	0.12	0.18	0.2
Guinea pig**	0.03	0.035	0.04	0.05	0.06	0.08	0.08	0.18	0.4
Human*	0.15	0	0.15	0	0.18	0.2	0.6	0.8	0
Human*	0.2	0	0.25	0	0.3	0.4	0.8	0	0
Human*	0.15	0.2	0.2	0.3	0.3	0.5	0.8	0	0
Human*	0.15	0.15	0.2	0.24	0.3	0.3	0.6	0.8	0

*Mixtures of complements from four or more guinea pigs; three or more persons.
**Single complements.

From the standpoint of fixability, no changes of deterioration were apparent in the majority of experiments until about the end of the second week when an increased susceptibility to nonspecific fixation by antigen alone and serum alone became apparent; by the end of the third week a slight decrease in fixability was usually apparent with a more marked susceptibility to the anticomplementary influences of serum and antigen alone as shown in Tables VIII and IX.

TABLE VIII

THE FIXABILITY OF UNDILUTED GUINEA PIG AND HUMAN COMPLEMENTS REPEATEDLY FROZEN AND THAWED

PRESERVATION	PIG		PIG		PIG		PIG		HUMAN		HUMAN	
	Wass.	Con.	Wass.	Con.	Wass.	Con.	Wass.	Con.	Wass.	Con.	Wass.	Con.
2 days.......	++++	—	++++	—	++++	—	++++	—	++++	—	++++	—
5 days.......	++++	—	++++	—	++++	—	++++	—	++++	++	++++	—
7 days.......	++++	—	++++	—	++++	—	++++	—	++++	+++	++++	+
9 days.......	++++	—	++++	—	++++	—	++++	—	++++	++++	++++	+
14 days.......	++++	—	++++	+	++++	—	++++	—	0	0	++++	++
21 days.......	++	—	++++	++	+++	+	++++	++	0	0	++++	++++

TABLE IX

THE FIXABILITY OF GUINEA PIG COMPLEMENT (UNDILUTED) REPEATEDLY FROZEN AND THAWED

PRESERVATION	UNIT OF COMPLEMENT	FIXATION SERIES						SERUM CONTROLS			ANTIGEN CONTROLS			HEMO. SYS.	SPECIFIC FIXATION
		1 U.	2 U.	3 U.	4 U.	5 U.	6 U.	1 U.	2 U.	3 U.	1 U.	2 U.	3 U.	1 UNIT	
Fresh......	0.03	++++	++++	++++	++	—	—	+	—	—	+	—	—	—	2 units
2 days.....	0.06	++++	++++	++++	++	—	—	+	—	—	+	—	—	—	2 units
3 days.....	0.06	++++	++++	+++	++	—	—	+	—	—	+	—	—	—	2 units
7 days.....	0.07	++++	++++	++	++	—	—	+	—	—	+	—	—	—	2 units
14 days.....	0.2	++++	++++	++++	++++	+++	+	+	+	—	+	+	—	—	2 units
21 days.....	0.3	++++	++++	++	+	+	—	+	+	—	+	+	—	—	1 unit

The hemolytic activity of human complement was preserved equally as well by this method as guinea pig complement, but increased susceptibility to nonspecific fixation set in much earlier being generally evident within the first week (Table VIII).

These experiments indicate quite clearly the importance of temperature in relation to the preservation of complement; a few experiments conducted with one portion of serum kept at 4° C. and a second portion at laboratory temperature have shown that marked deterioration in hemolytic activity with increased hypersensitiveness to the anticomplementary influences of serum and organ extract occurs within three days at the higher temperature in comparison to about two weeks or more at the lower. *With any method of preservation the serum should be kept at as low a temperature as possible and preferably in a frozen state in order to secure the best results.*

The Preservation of Undiluted Complement with 17 per cent Sodium Chloride.—In this method 0.17 gram of crystals of pure sodium chloride was dissolved in each cubic centimeter of serum and the mixture kept at 4° to 9° C.; when used each cubic centimeter of serum was diluted with 19 c.c. of distilled water yielding a 1:20 dilution of complement in isotonic saline solution.

Table X

The Hemolytic Activity of Guinea Pig Complement, Preserved with 17 per cent Sodium Chloride in a Refrigerator at 4° to 9° C.

PRESERVATION	UNIT OF COMPLEMENT				
	Serum 1	Serum 2	Serum 3	Serum 4	Serum 5
2 days	0.04	0.03	0.035	0.3	0.03
6 days	0.06	0.03	0.03	0.04	0.03
8 days	0.06	0.035	0.035	0.04	0.04
14 days	0.06	0.03	0.03	0.45	0.045
18 days	0.08	0.04	0.03	0.05	0.04
21 days	0.1	0.04	0.04	0.06	0.06
30 days	0.2	0.1	0.15	0.15	0.15

Table XI

The Fixability of Guinea Pig Complement Preserved with 17 per cent Sodium Chloride in a Refrigerator at 4° to 9° C.

PRESERVATION	RESULTS OF WASSERMANN TESTS									
	Wass.	Control	Wass.	Control	Wass.	Control	Wass.	Control	Wass.	Control
2 days	++++	—	++++	—	++++	—	++++	—	++++	—
6 days	++++	—	++++	—	++++	—	++++	—	++++	—
8 days	++++	—	++++	—	++++	—	++++	—	++++	—
14 days	++++	—	++++	—	++++	—	++++	—	++++	—
18 days	++++	—	++++	—	++++	—	++++	—	++++	—
21 days	++++	+	++++	—	++++	+	++++	—	++++	—
30 days	++++	++	++++	+	++++	+	++++	+	++++	+

The hemolytic activity was well preserved for at least three weeks; at the end of the first week the hemolytic unit was about equal to that of the same serum when fresh. At the end of the second week the unit was about one-half more; at the end of the third week about double, and after one month from three to five times greater than the unit of fresh serum (Table X, Chart 2).

Fixability by mixtures of syphilitic serum and organ extracts usually remains unchanged for at least a month, but a slight increase of susceptibility to nonspecific fixation by serum alone and antigen alone is to be expected by the end of the third week and practically always at the end of a month constituting a striking example of the fact that the preservation of hemolytic activity alone is not a safe criterion for a preserved complement (Table XI).

The Preservation of Undiluted Complement with 8.5 per cent Sodium Chloride.—In this method 0.085 gram of crystals of pure sodium chloride were dissolved in each cubic centimeter of complement serum and the mixture kept at 4° to 9° C.; when required, each cubic centimeter was diluted with 9 c.c. distilled water, yielding a 1:10 dilution in isotonic saline solution.

The hemolytic activity of guinea pig complement was not preserved as well as it was by 17 per cent sodium chloride described above; at the end of the second week the hemolytic unit was usually increased three or four times and at the end of three weeks about twelve times that of the same complements when fresh. Human complement showed similar results (Table XII, Chart 2).

Table XII

The Hemolytic Activity of Undiluted Complements Preserved with 8.5 Per Cent Sodium Chloride and Kept at 4° to 9° C.

COMPLEMENTS	UNIT OF COMPLEMENT DILUTED 1:10					
	2 Days	5 Days	7 Days	9 Days	14 Days	21 Days
Guinea Pig..........	0.03	0.04	0.05	0.08	0.09	0.2
Guinea Pig..........	0.02	0.03	0.03	0.06	0.09	0.5
Human.............	0.15	0.18	0.18	0.25	0.6	0

Fixability by syphilitic serum and organ extract is shown in Table XIII; as a general rule increased susceptibility to nonspecific fixation by serum and antigen alone was apparent at the end of three weeks followed by a decrease in sensitiveness to specific fixability by mixtures of syphilitic serum and organ extract.

The Preservation of Complement with 4.3 per cent Sodium Chloride.—With this percentage sodium chloride preservation of guinea pig complement was less complete than observed with serum preserved with 8.5 per cent sodium chloride and distinctly less than with 17 per cent.

During the first week the hemolytic activity dropped one-half and at the end of the second week the hemolytic unit was at least five times higher than the unit of the same serum when fresh. Fixability was preserved unaltered for at least five days but at the end of one week began to decrease with increased hypersensitiveness to the anticomplementary activity of serum and extract (Table XIV).

Table XIII

The Fixability of Guinea Pig Complement Preserved with 8.5 per cent Sodium Chloride, and Kept at 4° to 9° C.

PRESERVATION	UNIT OF COMPLEMENT	FIXATION SERIES						SERUM CONTROLS			ANTIGEN CONTROLS			HEMO. SYS.	SPECIFIC FIXATION
		1 U.	2 U.	3 U.	4 U.	5 U.	6 U.	1 U.	2 U.	3 U.	1 U.	2 U.	3 U.	1 UNIT	
Fresh.......	0.03	++++	++++	++++	++	—	—	+	—	—	+	—	—	—	2 units
2 days.....	0.03	++++	++++	++++	+++	—	—	+	—	—	+	—	—	—	2 units
4 days.....	0.05	++++	++++	++++	++	—	—	+	—	—	+	—	—	—	2 units
7 days.....	0.05	++++	++++	++++	+++	±	—	+	—	—	+	—	—	—	2 units
14 days.....	0.07	++++	++++	+++	++	—	—	+	—	—	+	—	—	—	2 units
21 days.....	1.08	++++	++++	+++	++	+	+	+	+	+	+	+	—	—	1 unit

Table XIV

The Hemolytic Activity and Fixability of Guinea Pig Complement Preserved with 4.3 per cent Sodium Chloride and Kept at 4° C.

AGE OF COMPLEMENT	COMPLEMENT TITRATIONS 1:5							UNIT OF COMPLEMENT	RESULTS OF WASSERMANN TEST WITH SAME SERUM
	0.05	0.08	0.1	0.2	0.3	0.4	0.5		
Fresh...	S.H.*	M.H.	H.	H.	H.	H.	H.	0.1	Positive; fixation of 6 u.
3 days..	S.H.	M.H.	H.	H.	H.	H.	H.	0.1	Positive; fixation of 6 u.
7 days..	S.H.	M.H.	M.H.	H.	H.	H.	H.	0.2	Positive; fixation of 4 u.
14 days..	N.H.	N.H.	N.H.	S.H.	S.H.	S.H.	H.	0	0

*H. = complete hemolysis; M.H. = marked hemolysis; S.H. = slight hemolysis; N.H. = no hemolysis.

The Preservation of Complement with Sodium Chloride by the Method of Thompson at 4° to 9° C.—In this method complement serum diluted 1:1 is preserved with 4.1 per cent sodium chloride. In our experiments the mixtures were kept at 4° to 9° C. Thompson states that with this method he is able to preserve guinea pig complement for at least two weeks and in some instances the complement was found as active as ever after six weeks.

In our experience the method has proved satisfactory and the hemolytic activity of guinea pig and human complement sera were well preserved; at the end of two weeks the hemolytic unit was unchanged or about double that of the same sera when fresh, and at the end of three weeks the units were about three times higher (Table XV, Chart 2). Human complement was not preserved quite as successfully as that of the guinea pig.

Table XV

The Hemolytic Activity of Complements Preserved with Sodium Chloride by the Thompson Method and Kept at 4° to 9° C.

COMPLEMENTS	UNIT OF COMPLEMENT DILUTED 1:10					
	2 days	5 days	7 days	9 days	14 days	21 days
Guinea Pig............	0.03	0.05	0.05	0.06	0.06	0.08
Guinea Pig............	0.03	0.04	0.06	0.06	0.08	0.1
Human................	0.15	0.15	0.15	0.2	0.2	0.25

The fixability of guinea pig complement appears to be perfectly preserved for at least two weeks, but generally after three weeks the complements became sensitive to nonspecific fixation by serum and antigen alone and began to lose sensitiveness to specific fixation by mixtures of syphilitic serum and antigen (Table XVI). Human complement developed this hypersensitiveness to nonspecific fixation much earlier and usually between the first and second weeks of preservation and was not, therefore, as well preserved as guinea pig complement.

Table XVI

The Fixability of Complements Preserved with Sodium Chloride by the Thompson Method and Kept at 4° to 9° C.

PRESERVATION	GUINEA PIG		GUINEA PIG		HUMAN	
	Wassermann	Control	Wassermann	Control	Wassermann	Control
2 days	++++	—	++++	—	++++	—
5 "	++++	—	++++	—	++++	—
7 "	++++	—	++++	—	++++	+
9 "	++++	—	++++	—	++++	++
14 "	++++	—	++++	—	++++	++++
21 "	++	+	++++	++	++++	++++

The Preservation of Complement with Sodium Chloride after the Method of Austin.—In this method a 40 per cent dilution of complement serum is preserved with about 37 per cent sodium chloride; in our experiments the mixtures were kept at 4° to 9° C. Austin states that he is able to preserve complement in bulk by this method in an ice box for at least two to three weeks and for a month or two if the mixtures are sealed in ampules. The method was designed for the preservation of complement in 40 per cent dilution for use in the Noguchi test and in order to reduce the percentage of salt to tonicity a 0.6 per cent solution of sodium chloride is used in conducting the test instead of the usual 0.9 per cent solution.

Rhamy has reported unfavorably upon this method and Noguchi[16] states that with this degree of hypertonization preservation is only partially successful and that the complement deteriorates in a comparatively short time.

In our experience the hemolytic activity of guinea pig complement was generally well preserved; at the end of the first week the hemolytic units were higher than the units of fresh serum and at least double by the end of the second week and from two to four times higher at the end of three weeks (Table XVII, Chart 2). Human complement was not nearly so well preserved by this method; not infrequently marked deterioration had occurred within the first week.

TABLE XVII

THE HEMOLYTIC ACTIVITY OF COMPLEMENTS PRESERVED WITH SODIUM CHLORIDE BY THE AUSTIN METHOD AND KEPT AT 4° TO 9° C.

COMPLEMENTS	UNIT OF COMPLEMENT DILUTED 1:10					
	2 days	5 days	7 days	9 days	14 days	21 days
Guinea pig	0.04	0.04	0.05	0.06	0.07	0.08
Guinea pig	0.03	0.03	0.04	0.06	0.08	0.12
Human	1.0	2.0	0	0	0	0

The fixability of guinea pig complement was well preserved for at least ten days, after which the complements began to show undue sensitiveness to the serum and antigen alone; with human complement this change was frequently apparent within the first week of preservation (Table XVIII).

The Preservation of Complement with Sodium Chloride after the Method of Neill.—In this method by which each cubic centimeter of complement serum is preserved with 0.1 c.c. of a saturated solution of sodium chloride in distilled water (36 per cent), Neill states that the hemolytic activity of guinea pig complement is preserved undiminished for at least two weeks provided the mixtures are kept at a temperature not above 6° C. He describes a very simple and highly efficient ice box for this purpose which can be easily put together in any laboratory.

TABLE XVIII

THE FIXABILITY OF COMPLEMENTS PRESERVED WITH SODIUM CHLORIDE BY THE AUSTIN METHOD AND KEPT AT 4° TO 9° C.

PRESERVATION	GUINEA PIG		GUINEA PIG		HUMAN	
	Wassermann	Control	Wassermann	Control	Wassermann	Control
2 days	++++	—	++++	—	++++	—
5 "	++++	—	++++	—	++++	+++
7 "	++++	—	++++	—	0	0
9 "	++++	—	++++	—	0	0
14 "	+++	—	++++	+	0	0
21 "	+++	+	++++	++	0	0

In our experiments the mixtures were kept in an ordinary refrigerator with a temperature fluctuating between 4° and 9° C. and the method was found quite satisfactory. With guinea pig and human complements deterioration in hemolytic activity was very slight or did not occur at all during the first week, but at the end of two weeks the units were generally about double the units of the same serum when fresh (Table XIX, Chart 2).

TABLE XIX

THE HEMOLYTIC ACTIVITY OF COMPLEMENTS PRESERVED WITH SODIUM CHLORIDE BY THE NEILL METHOD AND KEPT AT 4° TO 9° C.

Complements	UNIT OF COMPLEMENT DILUTED 1:10					
	2 days	5 days	7 days	9 days	14 days	21 days
Guinea pig	0.04	0.06	0.06	0.08	0.08	0.09
Guinea pig	0.04	0.04	0.04	0.06	0.08	0.1
Human	0.15	0.15	0.18	0.3	0.35	0.4

The fixability of guinea pig complement was perfectly preserved for at least two weeks; after the third week hypersensitiveness to nonspecific fixation was frequently apparent. With human complement this hypersensitiveness to serum and antigen alone was apparent after the first week of preservation (Table XX).

TABLE XX

THE FIXABILITY OF COMPLEMENTS PRESERVED WITH SODIUM CHLORIDE BY THE NEILL METHOD AND KEPT AT 4° TO 9° C.

PRESERVATION	GUINEA PIG		GUINEA PIG		HUMAN	
	Wassermann	Control	Wassermann	Control	Wassermann	Control
2 days	++++	−	++++	−	++++	−
5 "	++++	−	++++	−	++++	−
7 "	++++	−	++++	−	++++	+
9 "	++++	−	++++	−	++++	+++
14 "	++++	−	++++	−	++++	++++
21 "	++++	+	+++	+	++++	++++

The Preservation of Complement with Sodium Acetate after the Method of Rhamy.—In this method one part of complement serum is preserved with one and a half parts of a 10 per cent solution of chemically pure sodium acetate in 0.9 per cent salt solution; Rhamy states that with this technic complement is preserved for at least ten days in a refrigerator. Noguchi[16] has reported favorably on the method for the preservation of human complement over a period of at least four days; Ruediger states that a marked loss in fixability occurs in three days.

In our experiments the preserved complements were kept at 4° to 9° C; over a period of five days the hemolytic activity of both guinea pig and human complements remained practically unchanged. At the end of the first week the hemolytic units were about double those of the same sera when fresh and from two to three times higher at the end of two weeks (Table XXI, Chart 2). Human complement was occasionally observed to show proportionately less deterioration than guinea pig complement.

TABLE XXI

THE HEMOLYTIC ACTIVITY OF COMPLEMENTS PRESERVED WITH SODIUM ACETATE BY THE RHAMY METHOD AND KEPT AT 4° TO 9° C.

COMPLEMENTS	UNIT OF COMPLEMENT DILUTED 1:10					
	2 days	5 days	7 days	9 days	14 days	21 days
Guinea pig	0.03	0.05	0.07	0.08	0.08	0.2
Guinea pig	0.04	0.04	0.08	0.08	0.1	0.3
Human	0.15	0.2	0.2	0.2	0.25	0.4

Fixability of guinea pig complement was well preserved for at least two weeks after which a decrease in specific fixability by mixtures of syphilitic serum and antigen and an increased sensitiveness to nonspecific fixation by extract and serum alone became evident; with human complement this hypersensitiveness to extract and serum was frequently apparent after the fifth day of preservation (Table XXII).

Table XXII

The Fixability of Complements Preserved with Sodium Acetate by the Rhamy Method and Kept at 4° to 9° C.

PRESERVATION	GUINEA PIG		GUINEA PIG		GUINEA PIG	
	Wassermann	Control	Wassermann	Control	Wassermann	Control
2 days....	++++	−	++++	−	++++	−
5 days....	++++	−	++++	−	++++	−
7 days....	++++	−	++++	−	++++	+
9 days....	++++	−	++++	−	++++	++
14 days....	++++	−	+++	−	++++	++++
21 days....	+	−	++	+	++++	++++

The Preservation of Complement with 4.3 per cent Magnesium Sulphate.—The addition of 0.43 gram of fine magnesium to each ten c.c. of guinea pig complement serum preserved the hemolytic activity when kept at about 4° C. for about five days; at the end of one week the hemolytic unit was three times that of fresh serum and at the end of two weeks about ten times higher.

Table XXIII

The Hemolytic Activity and Fixability of Guinea Pig Complement Preserved with 4.3 per cent Magnesium Sulphate and Kept at 4° C.

AGE OF COMPLEMENT	COMPLEMENT TITRATIONS 1:5							UNIT OF COMPLEMENT	RESULTS OF WASSERMANN TESTS WITH SAME SERUM
	0.05	0.08	0.1	0.2	0.3	0.4	0.5		
Fresh....	*S.H.	M.H.	H.	H.	H.	H.	H.	0.1	Positive; fixation of 6 u.
3 days..	S.H.	M.H.	H.	H.	H.	H.	H.	0.1	Positive; fixation of 5 u.
7 days..	S.H.	M.H.	M.H.	M.H.	H.	H.	H.	0.3	Positive; fixation of 3 u.
14 days..	N.H.	N.H.	N.H.	N.H.	S.H.	S.H.	S.H.	0	0

*H.=complete hemolysis; M.H.=marked hemolysis; S.H.=slight hemolysis; N.H.=no hemolysis.

Fixation began to decrease about the fifth day and had dropped very decidedly by the end of the first week with a coincident hypersensitiveness to the anticomplementary activity of serum and organ extract (Table XXIII).

These experiments indicate that magnesium sulphate is inferior to sodium chloride as a preservative for complement.

The Preservation of Complement with Glycerol after the Method of Ruediger.—In this method complement is preserved by adding one part of sterilized glycerol to three parts serum; Ruediger states that deterioration appears to be prevented for a few days. Fixability was found to be increased duing the first three days and on the seventh day is almost equal to that of fresh complement.

In our experiments the mixtures were kept at 4° to 9° C.; the hemolytic activity was found to take a sharp drop within twenty-four hours following the addition of the glycerol, rendering the hemolytic units of both guinea pig and human complement almost double the units of the same sera when fresh. After this time deterioration in hemolytic activity occured more slowly; at the end of one week the units were from two to three times higher than the units of the plain sera when fresh, and about ten times higher at the end of two weeks (Table XXIV, Chart 2).

TABLE XXIV

THE HEMOLYTIC ACTIVITY OF COMPLEMENTS PRESERVED WITH GLYCEROL AFTER THE METHOD OF RUEDIGER AND KEPT AT 4° TO 9° C.

COMPLEMENTS	UNIT OF COMPLEMENT DILUTED 1:10							
	Fresh	1 day	2 days	5 days	7 days	9 days	14 days	21 days
Guinea pig	0.03	0.05	0.05	0.06	0.08	0.15	0.3	0.4
Guinea pig	0.03	0.06	0.06	0.06	0.08	0.1	0.4	0.8
Human	0.15	0.45	1.0	2.0	0	0	0	0

TABLE XXV

THE FIXABILITY OF COMPLEMENTS PRESERVED WITH GLYCEROL BY THE RUEDIGER METHOD AND KEPT AT 4° TO 9° C.

PRESERVATION	GUINEA PIG		GUINEA PIG		HUMAN	
	Wassermann	Control	Wassermann	Control	Wassermann	Control
2 days	++++	—	++++	—	++++	—
5 "	++++	—	++++	—	++++	+
7 "	++++	—	++++	—	0	0
9 "	++++	—	++++	—	0	0
14 "	++++	—	++++	+	0	0
21 "	+	+	+++	++	0	0

As far as we could ascertain the specific fixability of guinea pig complement remained unchanged for about nine days, when an increased sensitiveness to the anticomplementary activity of serum alone and antigen alone became apparent; with human complement this change was usually apparent within five days (Table XXV).

The Preservation of Dried Complement.—That serum complements may be preserved for a time by drying has been shown by Noguchi and others; in the Noguchi method guinea pig complement is rapidly dried in a special filter paper and was originally offered as a convenient means for preserving and handling this constituent of the complement-fixation test for syphilis. Owing to rapid deterioration, the method has been generally abandoned.

In our experiments squares of special paper measuring 100 by 100 mm. were saturated with measured amounts of guinea pig complement serum and rapidly dried by fanning at a low temperature. Calculations of the amount of serum in measured amounts of paper showed that some deterioration in hemolytic activity had occurred in the process of drying. In each experiment the papers were cut into strips of five millimeters and kept in tightly stoppered tubes at 4° to 9° C.

The results of tests for hemolytic activity of complement papers in three experiments are shown in Table XXVI and indicate that deterioration is particularly rapid during the first three days after which changes in hemolytic activity occur more slowly. At the end of one week the unit was about six times greater than during the first twenty-four hours following the preparation of paper; at the end of two or three weeks the units were about ten times higher (Table XXVI).

TABLE XXVI

THE HEMOLYTIC ACTIVITY OF GUINEA PIG COMPLEMENT DRIED IN PAPER

COMPLEMENT	UNIT OF COMPLEMENT*	UNIT OF PAPER					
		1 day	3 days	5 days	7 days	14 days	21 days
Guinea pig	0.004	2x5 mm.	5x15 mm.	5x15 mm.	5x15 mm.	5x30 mm.	5x30 mm.
Guinea pig	0.006	3x5 mm.	5x16 mm.	5x20 mm.	5x20 mm.	5x40 mm.	5x45 mm.
Guinea pig	0.004	2x5 mm.	3x 5 mm	5x15 mm.	5x20 mm.	5x20 mm.	5x30 mm.

*In terms of undiluted serum.

The fixability of complement dried in filter paper was found to decrease slightly within a few days after preparation and then to hold quite steady for several weeks without developing hypersensitiveness to the anticomplementary influence of serum or extract (Table XXVII).

TABLE XXVII

THE FIXABILITY OF A GUINEA PIG COMPLEMENT DRIED IN PAPER

AGE	WASSERMANN TESTS					Serum Control	Antigen Control	Hemolytic System
	0.1	0.01	0.001	0.0001	0.00001			
Fresh serum	++++	++++	++++	++++	++	—	—	—
1 day	++++	++++	+++	+++	—	—	—	—
3 days	++++	++++	++	++	—	—	—	—
7 days	++++	+++	+	—	—	—	—	—
14 days	++++	++	+	—	—	—	—	—
21 days	++++	++	+	—	—	—	—	—

In additional experiments measured amounts of plain guinea pig complement serum, serum plus the addition of 1 per cent sodium chloride and serum plus 5 per cent magnesium sulphate, were rapidly dried at a low temperature on weighed dishes and the amount of each dried product calculated per cubic centimeter of fluid serum as previously described.

As a result of the drying process the hemolytic activity of the plain serum and the serum plus 1 per cent sodium chloride was generally reduced one-half, whereas very slight or no appreciable deterioration occurred with the serum plus 5 per cent magnesium sulphate, as shown in Table XXVIII. During the first week the hemolytic activity of the plain dried serum and the serum plus 1 per cent sodium chloride was reduced three to five times whereas serum dried with magnesium sulphate usually retained its hemolytic activity practically unaltered and with but slight deterioration up to the third week (Table XXVIII).

TABLE XXVIII

THE HEMOLYTIC ACTIVITY OF DRIED GUINEA PIG COMPLEMENT

DRIED COMPLEMENT	UNIT OF FRESH SERUM	UNIT OF COMPLEMENT 1:10					
		1 day	3 days	5 days	7 days	14 days	21 days
Plain serum	0.04	0.08	0.09	0.1	0.2	0	0
Sod. Chlor. Serum 1%	0.04	0.1	0.12	0.14	0.14	0.18	0.8
Mag. Sulp. Serum 5%	0.04	0.04	0.04	0.04	0.04	0.08	0.08

The fixability of these dried complements appeared to drop slightly within a few days after preparation and then held quite steady throughout a period of three weeks without developing hypersensitiveness to nonspecific fixation by serum or organic extract (Table XXIX).

TABLE XXIX

THE FIXABILITY OF A GUINEA PIG'S COMPLEMENT DRIED WITH 5 PER CENT MAGNESIUM SULPHATE

AGE	WASSERMANN TESTS					Serum Control	Antigen Control	Hemolytic System
	0.1	0.01	0.001	0.0001	0.00001			
Fresh Serum	++++	++++	++++	++++	++	—	—	—
1 day	++++	++++	++++	+++	+	—	—	—
3 days	++++	++++	++++	+++	—	—	—	—
7 days	++++	++++	++++	+++	—	—	—	—
14 days	++++	++++	++++	+++	—	—	—	—
21 days	++++	++++	++++	++	—	—	—	—

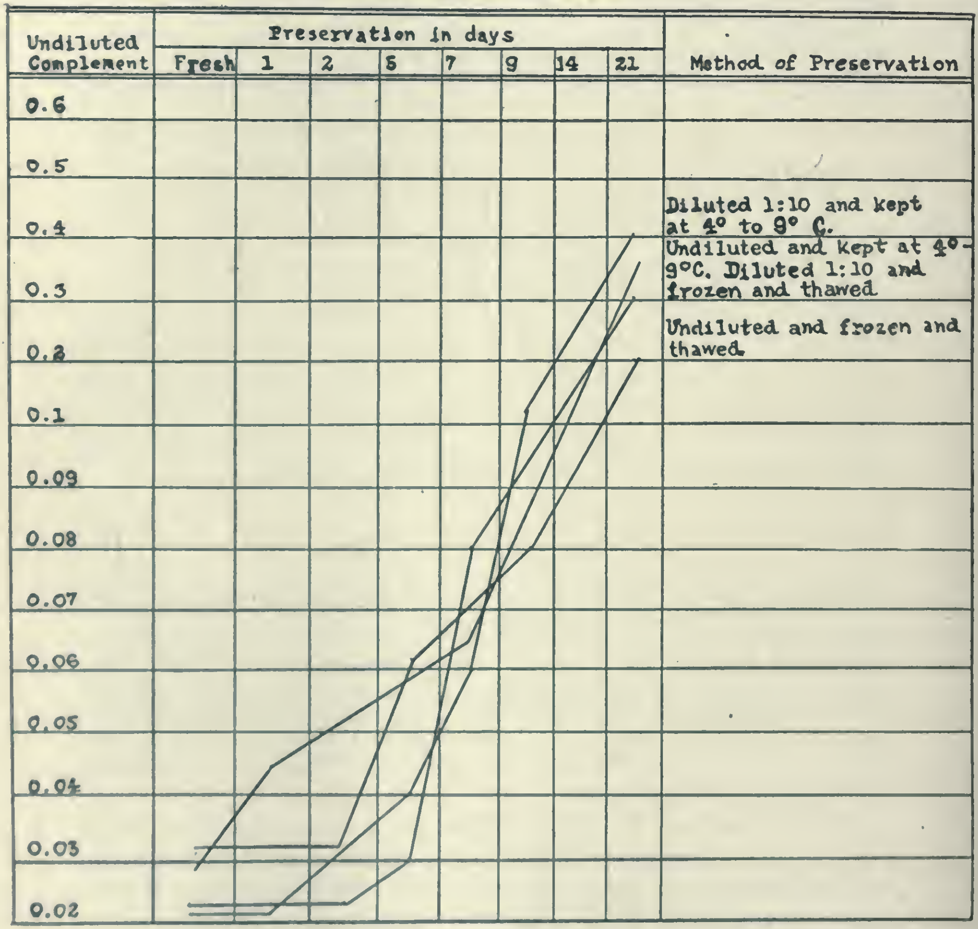
The drawbacks to the practical use of dried complement consist of the time and extreme care required in preparing the product and weighing it out as required, and the difficulty in securing clear solutions in distilled water or solutions of sodium chloride.

SUMMARY AND DISCUSSION

The sole object of our work was to determine by a series of comparative tests the practical value of various methods for the preservation of complement for conducting reliable Wassermann tests; several interesting theoretic considerations and discussions relative to the probable mechanism involved in the preservation of complement by various salts have been purposely omitted in order to emphasize the practical aspects.

Whatever method is used, temperature exerts a very important role and it is a well established general rule that complement serum should be kept as near the freezing point as possible. When complement is to be used in dilution of 1:10 the methods of Thompson and Neill are probably best, provided the preserved serum is kept near the freezing point; if complement is to be used in dilution of 1:20 the addition of 17 per cent sodium chloride and keeping at the freezing point preserves the serum in a remarkably efficient manner. Very probably sodium chloride is superior to magnesium sulphate and sodium acetate and apparently the best amounts to use are between 4 and 17 per cent; hypertonization does not appear to uniformly preserve complement as well as the lesser amounts of sodium chloride.

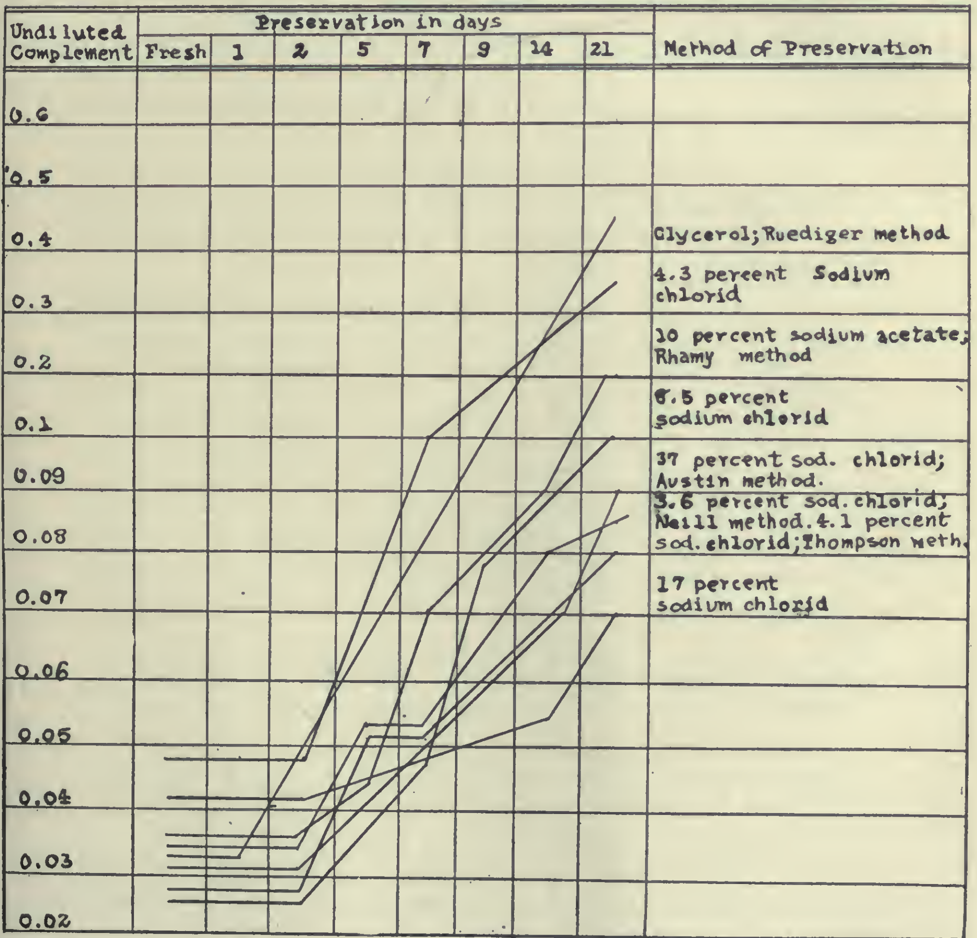
CHART I—The Hemolytic Activity of Guinea Pig Complement Preserved by Refrigeration.



Hemolytic activity alone is not a safe criterion for preserved complement as has been emphasized by Stillians;[17] it is well known that fresh complements vary in fixability and preserved complements are apt to lose in sensitiveness to fixation as they age, and more particularly acquire hypersensitiveness to the anticomplementary influences of serum and organ extract.

Charts 1 and 2 show in a general manner the deterioration of hemolytic activity of complements preserved according to the methods described; the results are only approximately correct inasmuch as the very nature of complement and the technic of the tests are such that absolute values can not be expressed. Not infrequently duplicate

CHART 2 — The Hemolytic Activity of Guinea Pig Complement Preserved with Sodium Chlorid, Sodium Acetate and Glycerol.



experiments yielded widely varying results due to inherent differences in the complement sera.

Table XXX shows a summary of our experiments bearing upon the fixability of preserved complements; in this table are given the days when the first changes in fixability became apparent. These changes were either an appreciable decrease in fixability by mixtures of syphilitic serum and organ extract or the first evidences of hypersensitiveness to the nonspecific fixation or anticomplementary influences alone of serum and extract. In judging the comparative merits of the different methods proposed for the preservation of complement we believe that it is more important to determine changes in fixability than in hemolytic activity. Deterioration in hemolytic activity can be compensated for by increasing the amount of serum, but even these larger amounts may be unreliable by reason of changes in fixability.

TABLE XXX

THE FIXABILITY OF GUINEA PIG COMPLEMENT PRESERVED BY VARIOUS METHODS

COMPLEMENT	PRESERVATIVE	TEMPERATURE	FIRST CHANGE IN FIXABILITY
1:10	0	4° to 9° C.	3 to 7 days
1:10	0	frozen and thawed	5 to 7 "
Undiluted	0	4° to 9° C.	7 to 10 "
"	0	frozen and thawed	14 to 21 "
"	17 per cent sodium chloride	4° to 9° C.	21 to 28 "
"	8.5 per cent sodium chloride	4° to 9° C.	14 to 21 "
"	4.3 per cent sodium chloride	4° C.	7 to 14 "
1:1	4.1 per cent sodium chloride (Thompson)	4° to 9° C.	14 to 21 "
1:1½	37 per cent sodium chloride (Austin)	4° to 9° C.	10 to 14 "
Slightly diluted	3.6 per cent sodium chloride (Neill)	4° to 9° C.	14 to 21 "
1:1½	10 per cent sodium acetate (Rhamy)	4° to 9° C.	7 to 14 "
Undiluted	4. 3 per cent magnesium sulphate	4° C.	5 to 7 "
1:3	glycerol (Ruediger)	4° to 9° C.	9 to 14 "
Undiluted	Dried in paper	4° to 9° C.	few days
"	Dried and powdered	4° to 9° C.	few days

We have endeavored to be conservative; undoubtedly better results could have been secured by keeping the sera at a lower temperature but 4° to 9° C. appealed to us as being a temperature most likely available in the majority of laboratories. In estimating the comparative merits of different methods for the preservation of complement we are guided by the results expressed in Table XXX taking the first day of changes in fixability as the criterion in using preserved sera.

A practical question of considerable weight concerns the advisability of depending on the fresh serum of one guinea pig for conducting a small number of Wassermann tests rather than employing a mixture of preserved complements. Undoubtedly fresh complement is always to be preferred and a single serum is to be chosen if tests for fixability are made, but if such preliminary tests can not be conducted, we believe that better work will be done with a mixture of complements preserved with sodium chloride at freezing temperature for a period not exceeding two weeks.

The hemolytic activity of human complement may be preserved as readily as guinea pig complement but changes in fixability and particularly an increased susceptibility to the anticomplementary influences of serum and organ extract, develop at a much earlier period.

CONCLUSIONS

1. Since a mixture of complements should be used in conducting Wassermann tests owing to variation in fixability of individual complements, a method for preserving complement constitutes a procedure of convenience and economic importance.
2. In judging the merits of preserved complement at least three values should be determined, namely, hemolytic activity, fixability by mixtures of syphilitic serum and extract and susceptibility to nonspecific fixation or the anticomplementary influences of serum and extract.
3. Changes in fixability and particularly increased hypersensitiveness to nonspecific fixation are probably more important criteria than changes in hemolytic activity.
4. Preserved human complement develops hypersensitiveness to nonspecific fixation more rapidly than guinea pig complement.
5. The temperature at which complement sera are kept exerts a marked influence; preserved complements should be kept as near the freezing point as possible and not above 4° C.
6. Of the sixteen methods studied in this investigation preservation with sodium chloride at a low temperature yielded the best results.

When complement is required in dilution of 1:10, the methods of Thompson and Neill are satisfactory for preserving guinea pig complement for a period of two weeks provided the serum is kept at a low temperature and preferably not above 4° C. When complement is required in dilution of 1:20 the addition of 0.17 gram sodium chloride to each cubic centimeter of serum and keeping at a low temperature preserves the complement for about three weeks.

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STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. VI

Human Versus Guinea Pig Complement in the Serum Diagnosis of Syphilis with Special Reference to Methods Employing Human Complement

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SINCE early in the history of the complement fixation test for syphilis various modifications have been proposed, utilizing the complement of each serum mainly for the purposes of economy, convenience, and the delicacy of reaction with unheated serum; at the present time a number of these tests are more or less widely employed and several utilize the natural hemolysis in human serum as well.

As part of our studies upon the standardization of the Wassermann test we have conducted a series of comparative tests with several of these modifications employing human complement in order to determine whether human complement is more reliable than guinea pig complement and to be seriously considered as the complement of choice in building up a standardized technic. Since a number of excellent tests employing human complement have been proposed, we have conducted this study largely by classifying these tests according to the principles involved and conducting our work with one or more of each class for the following purposes:

1. To compare human with guinea pig complement in the serum diagnosis of syphilis from the standpoints of *general adaptability, specificity and delicacy* and disregarding for the present the questions of economy, convenience and simplicity of technic.

2. To study the advantages and disadvantages inherent in the tests employing human complement.

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*This investigation has been conducted through the use of funds accumulated from the distribution of arsphenamine.

As shown in a preceding communication[1] human complement was found highly sensitive to fixation by mixtures of syphilitic serum and organ extract but likewise more variable in this property than guinea pig complement; furthermore, human complement was found more sensitive than guinea pig complement to the anti-complementary influences of serum and extract alone. The hemolytic activity of human complement is between six and seven times less that of guinea pig complement and contains variable amounts of agglutinin for various erythrocytes including human cells, which tend to interfere with hemolysis and reduce the practical value of human complement in a hemolytic system. Nevertheless, only trial and experience can determine the advantages and disadvantages of using human complement in a standardized technic and in this paper we are recording our experiences with a number of tests from these standpoints.

CLASSIFICATION OF COMPLEMENT-FIXATION TESTS FOR SYPHILIS EMPLOYING HUMAN COMPLEMENT

In the following classification the principles involved are stated with omission of technical details for the purpose of brevity; the references to original papers are given for anyone desirous of becoming acquainted with the technic.

First Class.—Methods utilizing the complement of each serum with immune hemolysins. In these tests each serum is used in a fixed dose for complement and fixing antibody (if present) with rabbit antihuman or antisheep hemolysins adjusted by titration and used in the main test in one or more units, or the hemolysins are used in fixed amount and the complement of each serum titrated for the unit of hemolytic activity and used in the main test in one or more units for complement and fixing antibody. The following tests may be placed in this category:

1. Tschernogubow[2] proposed the use of a suspension of the patient's blood directly diluted in saline solution in a ratio of one drop to one c.c. of saline to serve as complement, corpuscles, and, if present, the fixing antibody; owing to the enormous disproportion among the various elements and the tendency for coagulation this test has proved of little value and the author himself soon abandoned it.

2. Emery[3] employs a fixed amount of active serum as complement and fixing antibody with cholesterolized alcoholic extract of heart

muscle as antigen and rabbit antihuman amboceptor; the tests are carried out in capillary tubes.

3. Thompson[4] titrates each serum for hemolytic activity with one unit of rabbit antihuman hemolysin and 0.2 c.c. of a 2 per cent suspension of washed human cells; in conducting the main tests each serum is employed in dose of two units to furnish the complement and fixing antibody, if the latter is present. An extract of acetone insoluble lipoids is used for antigen.

4. Ronchese[5] uses each serum in dose of 0.2 c.c. as complement and for fixing antibody and titrates the antihuman amboceptor with 0.1 c.c. of 1:4 suspension of washed human cells.

5. Noguchi, in his newer test, uses each serum in a fixed dose of 0.1 c.c.,[6] or 0.2 c.c.[7] for complement and fixing antibody with an extract of acetone insoluble lipoids for antigen; rabbit antihuman hemolysin is titrated with 0.1 c.c. of 10 per cent human cells and 0.1 c.c. or 0.2 c.c. human complement and used in the main test in amount equal to one unit, unless hemolysis is deficient when more amboceptor is added.

6. Bronfenbrenner and Schlesinger[8] sensitize washed human cells with varying amounts of amboceptor and titrate the suspension with 0.025 c.c. human serum complement; in conducting the tests the cells are sensitized with ten units of amboceptor and used in a fixed dose. The complement activity of each serum is then titrated, and if found inactive, guinea pig complement is employed in the test. The main tests are conducted with 0.05 c.c. human serum for complement and fixing antibody with an extract of acetone insoluble lipoids as antigen.

7. Stern[9] employs each serum in a constant amount to furnish complement and the fixing antibody if the latter is present; sheep cells and antisheep hemolysin are employed, the latter in three to four units to avoid false positive reactions. Plain alcoholic extracts of heart muscle are used as antigen.

Second Class.—Methods employing human serum complement of healthy nonsyphilitic persons with heated sera instead of guinea pig complement.

1. Butler and Landon,[10] Myer [11] and Cress[12] have devised tests of this class for use on board ships which are essentially similar to the original Noguchi test except that human complement is used instead

of guinea pig complement. The sera for diagnosis are used active or after heating at 56° C. for one-half hour with an extract of acetone insoluble lipoids and an antihuman hemolytic system.

2. The newer test of Noguchi[7] for heated sera and spinal fluids is essentially similar; the sera are used in dose of 0.2 c.c. and spinal fluids in 0.2 to 0.5 c.c., complement being furnished by the serum of a healthy nonsyphilitic person in dose of 0.1 c.c. An extract of acetone insoluble lipoids is used as antigen with an antihuman hemolytic system.

3. Health[13] used the fresh active serum of persons for complement and an antisheep hemolytic system; the complement is employed in the same manner as guinea pig complement being titrated with sheep cells and antisheep hemolysin and employed in the main tests in two units.

Third Class.—Methods utilizing the complement as well as certain natural hemolysins of each serum. In these tests each serum is used in a fixed dose for complement, fixing antibody (if present) and hemolysin or each serum is titrated for hemolytic activity for certain erythrocytes and used in the smallest amount producing complete lysis of the test dose of cells. When complement is deficient guinea pig serum or the serum of a healthy nonsyphilitic person may be used for correction; if hemolysin is deficient or absent immune rabbit hemolysin may be added to correct the deficiency.

1. Tschernogubow[14] employs each serum in a fixed dose for complement-fixing antibody (if present) and natural antiguinea pig hemolysin. Plain alcoholic extracts of heart are used for antigen and washed guinea pig cells in a fixed dose for indicator antigen, taking advantage of the fact that over 90 per cent of human sera contain thermolabile hemolysin for these cells. Gurd[15] has modified this test by titrating the hemolytic activity of each serum with varying amounts and a fixed dose of guinea pig cells and has reported very favorably upon its practical value.

2. Foix[16] has described a test employing the complement of each serum with washed rabbit erythrocytes for indicator antigen utilizing the natural amboceptors for rabbit cells present in a large proportion of human cells.

3. Hecht* [17, 18, 19, and 20] and Flemming[21] utilize the complement and

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*In referring to the Hecht test most authors associate the name of Weinberg and designate the test as the Hecht-Weinberg; we have been unable to verify the references given to the Hecht-Weinberg reaction and found them as stated in the bibliography of this paper, in which all papers were by H. Hecht.

natural antisheep hemolysins of human sera; each serum is used in a fixed dose with varying doses of crude alcoholic extracts of heart as antigen. A fixed amount of washed sheep erythrocytes is used for indicator antigen on the basis that over 90 per cent of active human sera contain natural antisheep hemolysin.

4. Gradwohl[22] has modified and greatly increased the value of the Hecht test in such manner that the hemolytic activity of each serum in dose of 0.1 c.c. is measured by titration with increasing amounts of washed sheep blood; Burdick[23] and Bruce[25] have described further minor modifications embracing the principle of Gradwohl's modification.

5. Bartlett and O'Shansky[26] titrate the hemolytic activity of each serum for sheep cells by using each serum in increasing doses with a constant amount of washed sheep cells; the main test is conducted with the amount of serum just giving complete hemolysis and without preliminary incubation at 37° C. for complement fixation. Provisions are made for testing sera deficient in hemolytic activity.

SCOPE OF INVESTIGATION

In our studies which have been conducted during the past several years, the following tests have been included:

1. Tests of the first class. (a) A modification of the Emery test, essentially similar to that of Ronchese and the newer Noguchi homohemolytic test; the tests of (b) Thompson and (c) of Bronfenbrenner and Schlesinger.

2. Tests of the second class. (a) The Noguchi homohemolytic test with heated sera and unheated cerebrospinal fluids.

3. Tests of the third class. (a) The Hecht-Gradwohl test; (b) the Tschernogubow test so modified that the hemolytic activity of each serum for guinea pig cells is measured by titrating each serum in constant dose of 0.1 c.c. with increasing doses of a 5 per cent suspension of cells after the principle of the Gradwohl test and (c) the test of Bartlett and O'Shansky modified to include a primary period of incubation of one-half hour at 38° C.

For comparison each serum was tested with the regular Wassermann reaction employing the sera of three or more guinea pigs for mixed complement and with three antigens, one of which was always a cholesterolized alcoholic extract of either human or beef heart.

All sera were employed within seventy-two hours of the time of collection being kept at 4 to 9° C.; the majority were used within thirty-six hours of the time of collection.

While the authors of the various tests listed above have made provisions for carrying out their tests with such sera as may be deficient in complement or hemolysin by adding either human or guinea pig complement and immune hemolysin, we have not made these corrections in our work, but confined ourselves to following the technic as described by the various authors in the published accounts referred to insofar as their tests could be conducted with individual sera; any sera found deficient in complement, natural hemolysin or both was recorded accordingly and dropped.

PERCENTAGE OF HUMAN SERA CONTAINING SUFFICIENT COMPLEMENT FOR SPECIAL TESTS

Of primary importance in this connection is the percentage of human sera containing sufficient complement for these special tests.

Thompson[4] states that at least 98 per cent of human sera contain sufficient complement for the conduct of his test; Noguchi[7] found 92 to 97 per cent of sera to contain sufficient for his homohemolytic test. Kolmer[27] with a modification of the Emery test similar to that of Ronchese and Noguchi, found about 93 per cent of sera available. Bronfenbrenner and Schlesinger have not stated what percentage of human sera contain sufficient complement for their test.

Gradwohl[28] states that about 98 per cent of sera contain sufficient complement and natural antisheep hemolysin for the conduct of his modification of the Hecht test; Kolmer[24, 27] found about 92 per cent sufficiently hemolytic in two series of tests and Bartlett and O'Shansky found no index at all with 14 per cent of sera.[26] Bruce,[25] who employs a Hecht-Gradwohl test, found about 92 per cent of sera sufficiently hemolytic and Bartlett and O'Shansky[26] about 92 per cent sufficiently hemolytic for their test. Wade[29] has found about 96 per cent of sera hemolytic for guinea pig cells.

In our work the following percentages of human sera were found to contain sufficient complement, natural hemolysins or both for the special tests; as previously stated all sera were tested within seventy-two hours of the time of collection of blood and we believe that the results express the percentage of sera which may be expected to be satisfactory under ordinary routine conditions and without any special precautions against deterioration. The percentages given are based upon from 117 to 166 tests with each method:

Thompson test: 93 per cent (sera titrated in amounts ranging from 0.1 to 0.4 c.c. of 1:1 dilution; higher doses not employed which would have raised this percentage).

Noguchi homohemolytic test: 90 per cent.

Bronfenbrenner-Schlesinger test: 96 per cent.

Hecht-Gradwohl test: 91 per cent.

Bartlett-O'Shansky test: 90 per cent.

Modified Tschernogubow test: 88 per cent.

According to our results, therefore, at least 2 to 10 per cent of human sera do not contain sufficient complement, natural hemolysin or both for the conduct of these special tests and must either be dropped or conditions corrected by the addition of guinea pig or human complement or immune rabbit hemolysin.

COMPARATIVE RESULTS IN THE SERUM DIAGNOSIS OF SYPHILIS OF METHODS EMPLOYING HUMAN COMPLEMENT AND THE WASSERMANN TEST WITH GUINEA PIG COMPLEMENT

To base an opinion of the value of any or all of the special tests employing human complement upon the results of comparison with the Wassermann test is obviously a faulty method for evaluation of the status of these special tests; on the other hand, histories and clinical opinions are so frequently indefinite, misleading or varied that comparison with a good Wassermann test in which years of experience and critical clinical judgment have resulted in building up considerable confidence in its results and particularly from the standpoint of positive reactions indicating the presence of syphilis, appears to be the better method and particualrly when combined with special studies of such persons whose sera yield dissimilar results in the Wassermann and special tests.

Thompson has given no data on the comparative results with his test; Noguchi[7] did not conduct Wassermann tests, but states that of 1118 specimens of sera tested after his homohemolytic method 517 yielded positive and 601 negative reactions "the results conforming to those reported by the serological departments of the various hospitals" furnishing sera. Kolmer[27] with a test similar to that of Noguchi found 92 per cent of active sera yielding reactions in agreement with the Wassermann test; 8 per cent gave positive results with the special test and negative Wassermann reactions. With inactivated sera Kolmer found that 85 per cent of sera yielded similar results, 14 per cent yielded positive reactions with the special test and negative Wassermann reactions.

Gradwohl has never given figures comparing the results of his test with the Wassermann test, but states that his test has never been negative with a Wassermann positive serum and that whenever his test was positive and the Wassermann negative he had reasons for believing that the results of his test were correct and indicative of greater delicacy. Kolmer[24] found that the Hecht-Gradwohl and Wassermann tests agreed with 82 per cent of sera; with 16 per cent the special test was positive and the Wassermann negative, while in 2 per cent the Wassermann was positive and the special test negative. In a second series of comparative tests[27] similar results were observed. Bartlett and O'Shansky[26] report that the results of their test agreed with the Wassermann with 95 per cent of sera; 1 per cent gave a positive Wassermann reaction while with the special test the results were negative and 3 per cent yielded negative Wassermann reactions with positive results in the special tests. Bruce,[25] with the Hecht-Gradwohl test, found that 94.8 per cent of sera yielded the same results as the Wassermann test conducted with active serum; with inactivated serum he states that his percentages were similar to those reported by Kolmer.

As previously stated our Wassermann tests were conducted with the mixed complement sera of guinea pigs and with three antigens; the results of comparative tests are shown in Table I. Since the special tests employing active human serum were conducted with extracts of acetone insoluble lipoids the results of the Wassermann tests shown are the reactions conducted with the same extracts; had we summarized the Wassermann tests on the basis of results observed with cholesterolized extracts the percentage of positive Wassermann reactions would be higher, and to the best of our knowledge, correctly so.

As shown in Table I, the Wassermann tests conducted with heated sera and guinea pig complements agreed with the special tests employing unheated sera and human complements with from 86 to 92

TABLE I

COMPARATIVE RESULTS OF WASSERMANN AND SPECIAL TESTS EMPLOYING EXTRACTS OF ACETONE INSOLUBLE LIPOIDS

SPECIAL TESTS	SERA EXAMINED	BOTH TESTS AGREE	WASSERMANN POSITIVE SPECIAL TEST NEG.	WASSERMANN NEGATIVE SPECIAL TEST POS.
Thompson	155	86%	4%	10%
Noguchi (active serum)	130	88%	2%	10%
Noguchi (heated serum)	145	87%	4%	8%
Bronfenbrenner-Schesinger	117	88%	5%	7%
Hecht-Gradwohl	155	90%	2%	8%
Bartlett-O'Shansky	130	92%	5%	3%
Modified Tschernogubow	166	86%	8%	6%

per cent of sera, the same antigens being employed in all tests. Of the 8 to 14 per cent of sera showing varying results the majority yielded negative Wassermann reactions and positive reactions with the special tests.

Of the sera yielding positive reactions with the special tests and negative Wassermann reactions, we believe that the majority were true reactions and indicative of greater sensitiveness for syphilis antibody on the part of the special tests inasmuch as the majority of the sera were from persons undergoing active treatment with arsphenamine in the clinic of Professor Schamberg; on the other hand all of these tests are capable of yielding a small and variable percentage of apparently pseudopositive reactions with the sera of persons whom we have no reason for suspecting as suffering with syphilis.

In our hands all of the special tests likewise yielded from 2 to 8 per cent falsely negative reactions as compared with the Wassermann reactions; we feel no hesitation in recording these facts inasmuch as the positive Wassermann reactions were undoubtedly correct. Theoretically it would appear impossible for the special tests correctly performed to yield these results, inasmuch as they are theoretically more sensitive than tests conducted with heated sera and guinea pig complements, but the fact remains that these special tests conducted more or less routinely may be expected to yield a small percentage of falsely negative reactions. In a former paper of this series[1] it was shown that human complements vary in fixability and that an individual complement may not be fixable at all at a certain time and with a certain antigen and we believe that *this variation in fixability is the biological explanation of negative reactions with the special tests employing the complements of sera from syphilitic individuals.*

RESULTS WITH SPECIAL TESTS EMPLOYING SPINAL FLUIDS AND HEATED SERA AND HUMAN COMPLEMENT

In tests of this character the sera for diagnosis are used after heating to remove traces of native complement and anticomplementary substances and complement is furnished by the fresh serum of a healthy nonsyphilitic person. In the tests of Butler and Landon, Myers and Cress, a 40 per cent dilution of complement is employed in an antihuman system after the original Noguchi technic; in our experience these tests gave unsatisfactory results due principally to the small dose of complement employed by reason of the fact that human complement is at least six times weaker than guinea pig complement. In the Noguchi homohemolytic test[7] the complement serum is used undiluted in dose of 0.1 c.c. with 0.2 c.c. of heated serum and 0.2 to 0.5 c.c. spinal fluid for diagnosis. Kolmer used this dose of complement with 0.1 c.c. heated serum for diagnosis, finding that results were better than when 0.2 c.c. serum was employed. Of 88 sera tested in this manner 24 per cent could not be read owing to interference of hemolysis in the controls; of the remaining sera 85 per cent yielded reactions agreeing with the Wassermann reactions while 14 per cent yielded negative Wassermann reactions and positive Noguchi reactions. Of these it was apparent that a few at least were very probably pseudo or falsely positive reactions. Of tests with twenty-two spinal fluids tested in dose of 0.5 c.c. the results could not be read with nine, or about 41 per cent, owing to nonspecific inhibition of hemolysis in the controls.

In the present series of tests conducted by heating sera at 56° C. for one-half hour and using them in doses of 0.2 c.c. with 0.1 c.c. of fresh human complement the results could not be read in about 30 per cent owing to incomplete hemolysis in the serum controls. *We ascribe these defective results to the presence of agglutinins in the human sera (sera for diagnosis, complement sera or both) for the corpuscles of the indicator antigen* as discussed in a former paper of this series;[1] similar tests after the technic of Health in which an antisheep hemolytic system is employed did not yield this high percentage of defective reactions.

Of the tests with 145 sera in which the results could be read 87 per cent yielded reactions agreeing with the Wassermann reactions; 8 per cent yielded negative Wassermann reactions with positive Noguchi reactions and 4 per cent positive Wassermann reactions in which the Noguchi tests were negative (Table I).

Of the 8 per cent Wassermann negative sera yielding positive Noguchi reactions, at least three sera were from nonsyphilitic persons and in our experiences this test is more apt to yield indefinite or nonspecific results than the test employing active serum. We have ascribed these results to the presence of agglutinins for the human erythrocytes of the indicator antigen and to the anticomplementary influences of the heated serum plus antigen upon the human complement, which is known to be more sensitive to these influences than guinea pig complement.

Of the small group of 4 per cent Wassermann positive sera yielding negative Noguchi tests, all were from persons undergoing treatment for syphilis; we ascribe these results to variation in the fixability of the complement employed rather than to an interference with fixation by indifferent serum proteins.

THE RELATION OF ANTIGEN TO TESTS EMPLOYING THE COMPLEMENT OF EACH SERUM

In our opinion for all tests employing human complement, that is, the complement of each serum, extracts of acetone insoluble lipoids (Noguchi and Bronfenbrenner) constitute the most acceptable antigens. As Noguchi has originally stated, crude or plain alcoholic extracts of tissues may yield a small percentage of falsely positive reactions with active serum ascribed to nonspecific fixation of complement by protein constituents in the extract; whether or not this is the true explanation we believe that comparative tests employing plain alcoholic extracts of tissues with and without the addition of cholesterin are more apt to yield positive reactions with the sera of nonsyphilitic persons than acceptable extracts of acetone insoluble lipoids. Results expressed in the form of percentages of such reactions with different antigens do not show the superiority of acetone insoluble lipoids as strikingly as individual instances with selected sera. Among those who have published accounts of such tests Thompson, Bronfenbrenner and Schlesinger, Noguchi, Kolmer, Cress, Butler and Langdon have preferred extracts of acetone insoluble lipoids; Hecht, Gradwohl and Health apparently use plain alcoholic extracts, while Bartlett and O'Shansky have used extracts with and without cholesterin and acetone insoluble lipoids and Emery cholesterolized extracts.

A second factor of importance concerns the method for determining the proper dose of antigen to employ. Hecht, Gradwohl and Bartlett and O'Shansky have not stated how the antigen is titrated for use in their tests; Kolmer uses known negative and syphilitic sera (active) for the anticomplementary and antigenic titrations respectively in titrating antigen for the Hecht-Gradwohl and Noguchi homohemolytic tests and Bruce employs a similar technic for the Hecht-Gradwohl test. Thompson likewise uses active normal and syphilitic sera for these titrations while Bronfenbrenner and Schlesinger and Noguchi apparently titrate with guinea pig complement.

Owing to the fact that human complement differs from guinea pig complement in fixability and particularly in susceptibility to nonspecific fixation, we believe that antigens employed in all tests utilizing human complement should be adjusted to any particular test by titration with human complement.

ADVANTAGES AND DISADVANTAGES OF TESTS EMPLOYING HUMAN COMPLEMENT

As a general result of these studies the advantages and disadvantages of tests employing human complement as compared with the regular Wassermann reaction employing guinea pig complement and an antisheep hemolytic system, may be expressed in general and also by the consideration of certain of the tests in particular.

The general advantages may be summarized as follows:

1. Increased delicacy of reaction due to the use of unheated serum. According to several investigators heating serum at 56° C. for half an hour results in the destruction of syphilis antibody; according to the results of special studies on this problem in these laboratories

to be published in a subsequent paper, this is undoubtedly true but not to the extent that some investigations would tend to indicate.

Aside from this question of the influence of heat upon syphilis antibody, tests employing human complement generally yield more strongly positive reactions than the Wassermann test employing guinea pig complement by reason of the fact that human complement is somewhat more fixable and at the same time more susceptible to the anticomplementary influences of serum and antigen alone which tend to intensify the positive reactions.

2. Guinea pigs are unnecessary.

3. With those tests employing an antihuman hemolytic system, human erythrocytes are readily available from the specimens of blood submitted for examination.

4. With those tests employing an antihuman system, natural hemolysins do not enter to disturb quantitative relations in the hemolytic system; special studies on the influence of natural antisheep hemolysin upon the results of complement fixation tests for syphilis conducted in these laboratories will be published in a separate communication but here it may be stated that this influence has been overemphasized by certain investigators advocating the antihuman hemolytic system.

The *general disadvantages* may be summarized as follows:

1. Active sera are more likely to yield nonspecific positive reactions than heated sera; the antigen employed bears an important relation to this subject as discussed above.

2. Human complement varies in fixability, and since each test depends upon the one complement or set of complements in the individual serum, a small percentage of sera from syphilitic persons may yield falsely negative results. In the Wassermann test employing a mixture of guinea pig complements this error is reduced and furthermore the complement may be titrated for fixability prior to being accepted for the Wassermann test.

3. The sera must be relatively fresh and used before the natural complement has deteriorated and before the thermolabile anticomplementary changes have developed. Even though sera are employed within forty-eight hours of the time of collection a small percentage are found so defective in complement that they can not be used unless activated by the addition of complement of a nonsyphilitic person

which may be troublesome or of guinea pig complement, which alters the nature of the reaction.

4. With tests employing the antihuman hemolytic system the presence of iso-agglutinins in the sera may interfere with the results and furthermore the preparation of potent antihuman hemolysin is usually a time-consuming and difficult procedure as compared with the ease of preparing antisheep hemolysins.

5. Human complement is not satisfactory when used with heated sera and spinal fluids and particularly so with an antihuman hemolytic system due to the presence of hemagglutinins and the susceptibility of human complement to anticomplementary influences.

6. With tests depending upon natural hemolysins as well as the complement of each serum, a small percentage of sera are deficient in hemolysin and must be either discarded or conducted with the addition of immune hemolysin. A further disadvantage of these tests is that there is no practical method for determining the amounts of complement and hemolysin in a serum separately although this objection is more theoretical than practical.

Of the tests which we have placed in the first class, that of Thompson has yielded the best results in our hands and we regard his technic as particularly satisfactory for tests employing the complement of each serum with an antihuman hemolytic system. His method for titrating the complement of each serum is excellent and the absence of this in Noguchi's test constitutes a defect inasmuch as the hemolytic activity of human sera varies enough to warrant titration instead of adopting a uniform dose and particularly so since deterioration of complement inevitably occurs with some sera during the course of routine work. Furthermore Thompson titrates the antigen with human complement which constitutes another advantage although difficult to evaluate in actual figures.

The test of Bronfenbrenner and Schlesinger is good if very potent antihuman hemolysin is available in order to avoid agglutination of the corpuscles during sensitization of the indicator antigen. We have experienced considerable difficulty with this phase of their test and while sensitization undoubtedly reduces the unit of complement as stated by them, yet agglutination has proved a troublesome factor in our hands, whereas Thompson's test yielded sharp and excellent results with the same hemolysins.

With tests of the third class utilizing not only the complement of each serum but certain natural hemolysins as well, that of Bartlett and O'Shansky has yielded best results in our experience when a primary period of incubation was used instead of omitting primary incubation as practiced by Bartlett and O'Shansky. Fixation of human complement by syphilis antibody and extracts of acetone insoluble lipoids is undoubtedly a rapid phenomenon as shown by Bartlett and O'Shansky, but in our experience one half hour incubation on a water-bath for fixation increases the percentage of true positive reactions.

The Hecht test is obviously defective because the amount of complement and hemolysin in an individual serum may be excessive for a fixed dose of sheep cells so that hemolysis results despite some fixation of complement by syphilis antibody; furthermore, either the complement or hemolysin may be absent, resulting in a defective result. The same objections are true of the original Tschernogubow test employing guinea pig cells.

In the Gradwohl modification of the Hecht test the fixed dose of serum may be too small to give a hemolytic index although this may be corrected by using a larger amount of serum; furthermore it has appeared to us that Gradwohl uses too small amount of indicator antigen which may permit hemolysis to occur even though a portion of complement has been fixed by the presence of syphilis antibody. For this reason we have used one half the hemolytic index of cells for each serum instead of the sliding scale advocated by Gradwohl. In this connection we should state that under these conditions one half hour in a water-bath for primary incubation is sufficient and preferable to a period of one hour inasmuch as human complement undergoes appreciable deterioration during the longer period of exposure.

SUMMARY AND CONCLUSION

1. Tests for the serum diagnosis of syphilis employing human complement have been divided into three classes: (a) Those employing the complement of each serum with immune antihuman or antisheep hemolysins; (b) those using the serum of a nonsyphilitic person for complement as a substitute for guinea pig complement and (c) those utilizing the complement and certain natural hemolysins in each serum.

2. Studies with tests representing these three classes have shown that at least 2 to 10 per cent of human sera do not contain sufficient complement, natural hemolysin or both for the conduct of these special tests.

3. Comparative studies employing tests representing these three classes and the Wassermann test, showed that the results agreed with from 86 to 92 per cent of sera, the same antigen being employed in all tests.

4. The special tests employing human complement yielded a higher percentage of positive reactions than the Wassermann test; the majority of these results were correct and indicative of superior delicacy.

5. Tests utilizing the complement of each serum are capable of yielding falsely positive reactions with the sera of nonsyphilitic persons and particularly with crude alcoholic extracts of tissues for antigen. Extracts of acetone insoluble lipoids were found best for tests of this character.

6. Tests utilizing the complement of each serum are likewise capable of yielding falsely negative results with the sera of syphilitic persons yielding positive Wassermann reactions, which are ascribed to the lack of fixability by the complements of these particular sera.

7. Antigens used in these special tests should be titrated with human instead of guinea pig complement.

8. Human complement is not as satisfactory as guinea pig complement for the conduct of tests employing heated serum and spinal fluids.

9. The advantages of tests employing human complement are (1) greater delicacy; (2) guinea pigs are not required, and (3) sheep not required if an antihuman system is employed. The disadvantages are (1) falsely positive reactions may occur; (2) falsely negative reactions may occur; (3) the sera must be fresh; (4) unsatisfactory with heated sera and spinal fluids; (5) complement, natural hemolysin or both may be absent from sera and (6) isoagglutinins may interfere in tests employing an antihuman hemolytic system.

10. Of the special tests placed in the first class, that of Thompson, and of those placed in the third class that of Bartlett and O'Shansky, proved most reliable.

11. Because of the disadvantages inherent in those tests employing human complement a standardized Wassermann test can not utilize

human complement; on the other hand a standardized test must aspire to the delicacy of these special tests in order to prove as sensitive as is possible with specificity.

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EARLY NEUROSYPHILIS ASYMPTOMATICA WITH REPORT OF OBSERVATIONS AND CASES*

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THE purpose of this paper is to review neurosyphilis as it is manifested in its beginning and to present early case histories of the disease. For it is in the early period of syphilis that the interest of the psychiatrist begins. Indeed, so close is the association between the psychiatrist and the syphilologist that it is incumbent upon the latter to have a psychiatric training. On the other hand, psychiatry follows the treatment of syphilis with the utmost interest. We have only to think of the paretics who are yearly carried off by the thousands in the flower of manhood, of the tabetics, of the other tertiary diseases of the nervous system, or, of the hereditary syphilitic diseases of the brain and cord. It is significant of this close association that the first who experimented with and used the Ehrlich Hatta remedy upon man were two psychiatrists.

Although our knowledge of neurosyphilis is not now complete, yet, with such data as are available one is enabled to visualize the process from its incipiency to its fatal stages, cerebrospinal syphilis or general paralysis.

LABORATORY EVIDENCE OF EARLY NEUROSYPHILIS

Instances of an abnormal spinal fluid in the presecondary period of syphilis are recorded in the literature.

The most recent and the largest number of cases examined in primary syphilis are reported by Carnaz.[1] This writer studied the spinal fluid in 76 patients. Of the 24 cases examined with a negative serum Wassermann, the average lymphocytosis was 2.4 per c.mm. It was greater than 5 per c.mm. (this number he considered pathologic) in 8 per cent of cases. The spinal fluid Wassermann was negative in all 24 cases. Of the 52 cases with a positive serum Wassermann, the average lymphocytosis was 6.1 per c.mm. It was greater than 5 in

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35 per cent of cases. The spinal fluid Wassermann was positive in one case which in addition presented a lymphocytosis of 9 per c.mm.

With[2] examined the spinal fluid in 45 cases of primary syphilis with a negative serum Wassermann reaction. Of this number one case presented a lymphocytosis over 10 cells per c.mm. (he considered a cell count of 4 or less as normal, and a count between 4 and 10 as suspicious; greater than 10 as definitely pathologic). The spinal fluid Wassermann was negative in all except this one case. Of the thirty-seven cases examined with a positive serum Wassermann, three presented a lymphocytosis over 10 cells. The spinal fluid Wassermann was negative in all. The spinal fluid of twenty cases of primary syphilis were examined by Dennie and Smith.[3] Of this number 6, or 30 per cent, had entirely negative serum Wassermann reactions, the spinal fluid was entirely negative. Ten, or 50 per cent, had four-plus Wassermann reactions on the serum and entirely negative spinal fluid. Four, or 20 per cent, had four-plus Wassermann reactions and mild spinal fluid findings (lymphocytosis of 4, trace of globulin and slight changes, never exceeding 2, in the first five tubes of the Gold-Sol test; negative Wassermann in all four cases).

The older and frequently quoted reports are the following: Wechselmann's[4] six cases of primary syphilis with spinal fluid findings indicative of an involvement of the nervous system. Sixteen cases were studied by Leopold[5] in whom six presented neurologic abnormalities as well as spinal fluid changes. In these cases some of the following subjective and objective symptoms were noted: headache, sensory changes, increased reflexes, Babinski's sign, Rombergism, inequality of pupils and difference in pupillary reactions. In seven cases suggestive neurologic abnormalities were noted. In these however the spinal fluid was normal. Three cases were entirely negative clinically and showed no abnormalities in the spinal fluid. In the 8 cases of Altmann and Dreyfus[6] 2 showed spinal fluid abnormalities. Wile and Stokes[7] studied 6 cases of primary syphilis. Neurologic abnormalities were present in 3 of the cases. Slight spinal fluid changes were found in 3 cases, and these changes were marked in a fourth case.

In the secondary period of syphilis, according to the reported observations, alterations in the spinal fluid occur in a large proportion of cases.

Gennerich[8] states that at some time, either before or during intensive salvarsan treatment, 90 per cent of his cases showed some abnormality of the spinal fluid. Ravaut[9] found abnormalities, with pleocytosis or globulin excess or both, in 67 per cent of cases; Altman and Dreyfus[10] in 66 per cent; Ellis and Swift[11] in 33 per cent; Robertson and Klauder[12] in 70 per cent. On the other hand, Fordyce[13] records less than 20 per cent as showing spinal fluid abnormalities in this period of the disease. In Carnaz's[14] series of secondary syphilitics the spinal fluid showed abnormalities in 40 per cent of cases; in With's[15] series 10 per cent of cases, and in Dennie and Smith's[16] series the spinal fluid showed slight abnormalities in 35 per cent of cases and marked abnormalities in 20 per cent.

From the above it is evident that there is no agreement as to the occurrence of abnormal findings in the spinal fluid in the early period of syphilis. This in part may be explained by the varying opinion concerning abnormal lymphocytosis in the spinal fluid. Different writers have chosen different standards. For instance, Isenegger[17] after examining a number of nonsyphilitic individuals with apparently normal nervous systems, concluded that the normal spinal fluid contains an average of 2.4 lymphocytes per c.mm. Bloch and Vernes[18] conclude that normally not more than 1 lymphocyte per c.mm. is found. In this review the standard normal lymphocyte content was according to Carnaz, 5; according to With, 10; whereas Dreyfus' standard was 1 to 5 normal; 6 to 9 doubtful; 10 to 20 slight lymphocytosis.

Unfortunately some of the papers do not contain details of technic. In some instances the simple statement appears, "Positive Globulin," without mention of the method used in its estimation or the standard used in its reading. Also with the Wassermann reaction, no mention was made of the antigen or amount of spinal fluid used.

Of the minor changes in the spinal fluid of early syphilitics, an increase of a few cells and a trace of globulin, it has been questioned by some writers whether these changes are sufficient evidence of a nervous system involvement at this period, or, do not more properly represent transient, evanescent, meningeal irritation. Those who hold this view are of the belief that only those cases which show conspicuous spinal fluid changes, are candidates for one or the other of the different clinical types of neurosyphilis. The number showing these changes is usually stated to be about 10 per cent. These figures closely agree with the stated percentage of syphilitics who later develop clinical neurosyphilis. About the only available data concerning the percentage of syphilitics who in later years develop one or the other clinical types of neurosyphilis, are the frequently quoted statistics of Mattauschek and Pilz.[19] These writers studied the records of 4,134 cases of army officers who had been infected during the two decades between 1880-1900, the investigators following their careers to the year 1911. They found that 4.75 per cent had developed general paralysis, 2.5 per cent, tabes, and about 3 per cent cerebrospinal syphilis. On the other hand, Ravaut[19a] is of the opinion that every change in the spinal fluid speaks for a disease of the nervous system. To these minor changes he applied the term "meningo-recidives histologique" in contradistinction to frank symptoms of meningitis. Of interest in this regard are the reported autopsy findings in the nervous system in secondary syphilitics. Zaloziecky[20] reports a case. Neurologically the patient was negative. The spinal fluid showed a pleocytosis, a Phase I reaction and a positive Wassermann reaction. The gross autopsy findings were negative. However, microscopic examination was not made. In Frankel's[21] case the neurologic examination was negative. The spinal fluid showed a positive Wassermann reaction. Macroscopic and microscopic examinations of the nervous system were negative, but, the writer adds, the microscopic examination did not extend over the entire nervous system.

Of importance in the analysis of early neurosyphilis are the reported instances of the finding of the Treponema pallidum in the spinal fluid of cases in the primary and secondary periods of the disease.

Marinesco and Minea[22] by means of animal inoculation demonstrated the presence of Treponema pallidum in the spinal fluid in 5 of 8 primary cases studied. Of the 5 positive cases it should be noted that the spinal fluid in 3 cases was entirely negative as to other findings; in 3 other cases, the fluid showed the presence of 3, 4 and 6 lymphocytes respectively, a negative globulin and Wassermann reaction; in the 2 remaining cases no mention was made as to the other fluid changes. The serum Wassermann reaction was negative in 2 of the 5 positive cases, and positive in the other three.

With a specimen of spinal fluid from a case of secondary syphilis Hoffman[23] scarified the eyebrow of a monkey. A chancre resulted at the site of scarification. In Steiner's[24] twenty cases of early syphilis he demonstrated the presence of treponema in the spinal fluid of three. In these three cases the spinal fluid was entirely negative as to pleocytosis, globulin and Wassermann reactions. Artz and Kerl[25] record finding the treponema in the spinal fluid in two of eleven primary and secondary cases studied. Frühwald and Zaloziecki[26] studied the treponema content of the spinal fluid from patients in the primary, secondary and tertiary periods of syphilis. Of the 23 cases examined, positive results were obtained in one primary and one secondary case, and also from a case of early meningitis and one of tabes. In the spinal fluid of a secondary syphilitic with a papular eruption who presented clinical and spinal fluid evidence of a nervous system involvement, Fildes, Roderick, Parnell and Maitland[27] demonstrated the presence of the treponema by dark-field examination. In five positive cases, the spinal fluid findings were not stated in two, definitely negative in three.

In the above series of positive cases the spinal fluid otherwise was found normal in some and abnormal in others. Subjective and objective symptoms on the part of the nervous system were sometimes present, and frequently absent. The serum Wassermann reaction was negative, but in some instances it was positive. There was thus no regularity in the findings so far as evidences of a nervous system involvement (other than the presence of treponema in the fluid) were concerned.

The Treponema pallidum has been demonstrated in the spinal fluid from cases in the post-secondary period, showing acute forms of neurosyphilis, by the following investigators: Nichols and Hough,[28] Gaucher, et al,[29] Reasoner,[30] Graves,[31] and Wile.[32] In late neurosyphilis the spinal fluid has been examined and reported negative for treponema by: Nonne, Ravaut, Graetz, Siebert, Neisser, Thibierge, Graves, and others. However, positive findings in the same type of cases have been reported by other writers. The author has not been able to find an instance of the demonstration of the treponema in the spinal fluid of tertiary syphilis unassociated with demonstrable involvement of the nervous system. When one considers the high percentage of cases in which the spinal fluid shows abnormal changes in the secondary period and the demonstration of Treponema pallidum in otherwise normal fluid in the same period of the disease, it is quite logical to assume that in every case of syphilis at the time of the acute treponememia the nervous system is invaded by the parasite.* In some instances (Artz and Kerl,[33] and Steiner[34]) it has been shown that this invasion occurred without causing other abnormalities in the spinal fluid and without clinical symptoms. The tissues of the nervous system viewed in this light did not apparently react to this invasion. Whether this lack of reaction is conditioned by the special characteristics and the virulence of the invading treponemata, or whether, independently of the latter, they are attributable to existing "disposition" of the tissues, can not as yet be definitely determined.†

It is plausible to assume that the nervous system may later react to early implanted foci of treponemata. The reaction at this would constitute an allergic phenomenon. Moreover, this view is strengthened by clinical observation concerning the role that trauma, infectious diseases and emotional stress and strain play as an exciting cause of paresis. Lang,[35] writing in 1880, was of the opinion that an organ which is the site of a gummatous lesion must have been affected in the early period of the disease. This opinion is shared by McIntosh and Fildes,[36] as expressed in the following statement: "A tertiary syphilitic lesion such as gumma is due to a recrudescence in a remnant of spirochete which has remained *in situ* since the generalization during the acute stage." It therefore appears that every syphilitic is a latent neurosyphilitic.

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*The invasion of the nervous system by Treponema pallidum is not characteristic of syphilis as a protozoon infection (it is perhaps generally accepted that Treponema pallidum is a protozoon). For it is now known that as soon as Trypanosoma Gambiense, the causative agent of sleeping sickness, has found its way into the spinal fluid, the central nervous system is affected.

†An involvement of the nervous system in experimentally produced syphilis in rabbits has been observed and studied by Weygandt and Jacob (Dermatol. Wchnschr., 1914, lviii, Ergangsbft., 150). These workers studied the route of infection of the nervous system, the histologic changes produced and the question of neurotropic strains of treponemata. They observed that after inoculating rabbits in the testicles, the brain or the intravenous routes, 50 per cent showed changes in the nervous system, and that these changes were the same, whichever route was adopted.

In some of the animals only the mesodermal coverings of the nervous system and their efferent vessels were the site of chronic exudative infiltration; in others, often in those injected with the same strain of Treponema pallidum there was evidence of diffuse processes, especially in the cortex; in addition they were also able to observe primary toxic parenchymatous degeneration, in rare instances developing unilaterally.

The experiments furthermore demonstrate that in some animals (4 of 29 receiving cerebral injections inoculated with the same strain of Treponema pallidum and treated exactly alike failed to present nervous phenomena) injections with totally different strains led to the same specific nervous manifestations in all.

These findings thus argue against the theory of a neurotropic strain of treponema, but they give no explanation of the important problem why treponemata of the same strain lead to nervous symptoms in some instances and not in others.

The authors nevertheless are able to conclude that strains of treponemata of very pronounced virulence are particularly prone to lead to severe and diffuse affections of the nervous system, especially in the brain, and that such symptoms appear decidedly earlier than those produced by benign strains of treponemata.

Histologically the changes in the central nervous system in experimental syphilis show a close relationship with meningoencephalitis luetica in the human subject, and at many points in the cortex the changes suggest similar phenomena associated with progressive paralysis, especially with regard to evidences of injury and of primary parenchymatous degeneration which accompany the inflammatory infiltration. In individual instances the authors observed changes with pronounced parenchymatous and endarteritic characteristics in the small cerebral vessels, suggesting a certain resemblance to endarteritic cerebral lues.

CLINICAL EVIDENCE OF EARLY NEUROSYPHILIS

The clinical symptoms of a nervous system involvement in the secondary period of syphilis were recognized long before the introduction of the lumbar punture by Quincke in 1891. Such symptoms were first described by Guarinone[37] writing in 1610, and since then by many of the other earlier writers—Lang, Nonne, Neisser and notably Fournier. This syphilologist in his *Lecons Cliniques sur la Syphilis* describes in detail the nervous manifestations present in secondary syphilis—headache, dizziness, torpor, paresthesiæ, areas of analgesia and hypalgesia, etc.

The symptoms of neurosyphilis in the secondary period of the disease are usually referable to an involvement of the meninges. This involvement may be acute or subacute, localized or diffuse and may be divided into three clinical types:

1. All the characteristic symptoms of an acute cerebrospinal meningitis even with opisthotonus.
2. An acute psychosis, characterized by excitement, disorientation, confusion, some memory defect, delusions and possibly hallucinations. This type is seen in Case No. 5, although the patient was not in the eruptive stage, yet comparatively recently infected.
3. Headache.

To these may be added a fourth or asymptomatic group. In this group, although the spinal fluid shows very conspicuous evidence of a meningeal involvement, yet clinically there are no subjective or objective evidences (Cases No. 1 and 2).

Associated with the first three types, some or all of the following neurologic abnormalities may be noted: Exaggeration of the superficial and deep reflexes, Babinski's sign, Rombergism, pupillary abnormalities and sensory changes.

Types three and four are by far the most common. Indeed, the classical and well-known symptom of headache in the eruptive period of syphilis is always meningeal in origin. Not infrequently it is the only symptom present. In some cases insomnia and mild depression may be associated with headache. It may be slight or severe, "head-splitting" in character. It is the existence of the asymptomatic type of neurosyphilis that makes it incumbent to examine the spinal fluid in order to properly diagnose and treat syphilis at an early period.

Parenchymatous and vascular lesions of neurosyphilis may occur in the early period of the disease, but are exceptional (see Cases No. 6 and 7).

Of the cranial nerves in early syphilis, the eighth and second are most frequently affected. Crockett[38] in 1897 was the first to call attention to the early involvement of the eigth nerve in syphilis, but little significance was laid by this writer upon its importance.* Indeed this early involvement remained a neglected diagnostic sign until Wanner[39] as well as Beck[40] in 1913 again called attention to this involvement as being of great value in the early diagnosis of syphilis. Wanner was able to make a diagnosis of syphilis in 95 per cent of the early cases he examined, before the appearance of any generalized symptoms. The diagnosis of syphilis in these cases was later confirmed by clinical and laboratory findings. Many writers have since reported a very high percentage of involvement of this nerve in the early period of syphilis. In Knick's and Zaloziecky's[41] series of cases, the spinal fluid showed abnomalities in all the cases presenting an eighth nerve involvement. These writers, therefore, concluded that this involvement was due to a syphilitic infection of the nerve sheath. The involvement of the eighth nerve may arise directly, a syphilitic process originating in the nerve—a neuritis, or, by the presence of a syphilitic exudate or infiltrate, or indirectly, pressure due to narrowing of the bony canal or the presence of a basilar meningitis.

In the majority of instances both divisions of the nerve are involved, the cochlear branch often to a greater degree than the vestibular, and the involvement is usually bilateral. Clinically the involvement of the cochlear is characterized by normal conversational tone perception, a shortening of the duration of perception, by bone conduction out of all proportion to the shortening of the duration of perception for the same fork by air conduction and the retention of good hearing for the low forks, with a loss of perception, or a reduction in duration of perception, for sounds of high pitch.†

In addition to these characteristic findings of a cochlear involvement, symptoms referable to an involvement of the vestibular and semicircular canals may be present. These symptoms are tinnitus, vertigo and vomiting. Indeed, symptoms of cochlear, vestibular, facial and trigeminus nerve irritation may occur at this period of syphilis, the so-called ''Frankle-Hochwarts'' disease or ''Polyneuritis cerebralis Menieriformis.''

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*Schwartze in 1869 pointed out that an impairment in the conduction of sound through the bones of the skull occurs regularly at an early period of syphilis. He attributed this impairment to a syphilitic catarrhal inflammation in the middle ear. (Quoted by Taylor: Venereal Diseases, Lea Brothers & Co., 1895, p. 711).

†It is of importance to note that deafness therefore is not a necessary complaint in the presence of an eighth nerve involvement. For the application of this test see the comprehensive paper, "The Diagnostic Value of Lowered Bone Conduction in Syphilis," Groeckerman, Barlow, and Stokes, Am. Jour. Syph., 1919, iii, No. 2, p. 241.

Involvement of the second nerve in the early period of syphilis is manifested as an optic neuritis. In my experience this involvement is frequently noted in association with other neurological evidences of a nervous system involvement and rarely as isolated evidence.

Involvement of the third, fourth, fifth, sixth, and seventh nerves in the early period of syphilis are most frequently observed as a neurorecidive. In Benario's[42] series of 116 cases of neurorecidive, the cranial nerves were involved in the following proportion: auditory, 43 per cent; optic, 26 per cent; facial, 15 per cent; the remainder divided among the motor oculi, the patheticus, the trigeminus and the abducens. From clinical observations and from Benario's statistical study it becomes apparent that the eighth nerve is the most frequently involved nerve in the so-called neurorecurrence or neurorecidive. Ehrlich[43] compares the involvement at this time to the local reaction (Herxheimer reaction) seen in secondary syphilides after an injection of arsphenamine. He is of the opinion that after arsphenamine therapy there occurs a local reaction and swelling in the region of the nerve and the resulting pressure on the nerve is responsible for the nerve symptom. Appropriate mention may be made of an unusual case recently seen, a neurorecidive manifested in an involvement of the eighth nerve. The patient complained of headache, deafness, tinnitus and vomiting, and experienced an epileptiform seizure. The pupils were unequal but reacted to light, the right patellar reflex was lively, the left normal, the station showed Rombergism. The spinal fluid was negative. From the findings elicited by Barany's test the symptoms were regarded as due to a hemorrhage in the semicircular canals.

REPORT OF OBSERVATIONS

In a series of 25 cases an initial examination of the spinal fluid was made in the untreated eruptive stage of syphilis and a second one after the administration of four intravenous injections of arsphenamine .5 gm. at seven to ten day intervals. No other treatment was administered. In each case after the first administration of arsphenamine an accentuation of the eruption was noted—a Herxheimer reaction. It was observed in one case, an individual with a diffuse macular syphilide who complained of headache, with lively patella reflexes but otherwise neurologically negative, that a spinal fluid lymphocytosis of fifteen remain unchanged after the above treatment. The spinal fluid otherwise was negative in both the first and second examination. In another case (neurologic and spinal fluid examinations negative), there developed after the above treatment, a spinal fluid lymphocytosis of twenty and a positive globulin reaction (Noguchi). The four-plus serum Wassermann remained unchanged Spinal fluid Wassermann negative on the first and second examinations. A third case, (neurologic and spinal fluid examinations negative), complained after the fourth injection of arsphenamine of a severe headache. The spinal fluid at this time showed a lymphocytosis of eighty, positive globulin reaction (Noguchi), the Wassermann with a cholesterolized antigen with 1 c.c. of fluid was negative,* but subsequently became four-plus. The four-plus serum Wassermann reaction remained unchanged. After the continuation of treatment the headache disappeared and the spinal fluid became normal. This occurrence—a neurorecidive in the course of arsphenamine therapy—is not rare. The noteworthy feature is that before treatment the spinal fluid was negative.

REVIEW OF LITERATURE. SIMILAR CASES. NEURORECIDIVE AND HERXHEIMER REACTION

The above observations are similar to those made by Altman and Dreyfus.[44] They examined the spinal fluid in the primary and secondary period of syphilis before and after the administration of 1.5 gm. of salvarsan given in the course of about three weeks. They observed that slight changes in the spinal fluid before treatment would become negative after treatment. In one instance the findings remained unchanged, and in another they were markedly improved. Of particular interest are their observations upon one case which presented no subjective or objective symptoms of a nervous system involvement and whose spinal fluid was negative. This patient received .4 gm. of salvarsan intravenously after which he absented himself from the clinic. However, seven weeks later he returned. At this time he presented a facial paralysis and an involvement of the eighth nerve. The spinal fluid showed a high pleocytosis, marked presence of globulin and a positive Wassermann reaction in both high and low dilutions of spinal fluid. The serum Wassermann on both examinations was four-plus. These writers speak of this phenomenon as a provocative neurorecidive.

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*Cholesterolized heart antigen and 1 c.c. of fluid were used in all Wassermann reaction reported in these observations.

Neurorecidive or neurorecurrence is the occurrence in the earlier period of syphilis of a clinical manifestation of neurosyphilis, usually meningeal in nature, with or without an involvement of a cranial nerve, and appearing in the course of arsphenamine therapy. More frequently, however, it occurs after insufficient treatment with arsphenamine and the cessation of all other treatment. At the time of the neurorecidive the spinal fluid shows a high pleocytosis, marked presence of globulin and a positive Wassermann. The serum Wassermann invariably remains unchanged.

The above observations are in accordance with the hypothesis of Generich,[45] that salvarsan has a provocative influence upon changes in the spinal fluid in cases of primary syphilis.

Ehrlich explained the occurrence of neurorecidive upon an immunologic basis. He pointed out that, "In these patients the greater part of the infecting organism has been destroyed by the powerful spirocheticidal action of the salvarsan. So rapidly has this been accomplished that the usual tissue immunity which develops as a result of prolonged contact between parasite and host is lacking, as a result a small focus of spirochetes in the tissues of the central nervous system, thus escaping the spirocheticidal action of the salvarsan, can develop in the susceptible host with great rapidity and severity." Artz and Kerl[46] state that, "Since treponemata are found in the spinal fluid in early syphilitics we can conclude that neurorecidive is due to activating latent groups of treponemata."

Nonne[47] summarizes this phenomenon of neurorecidive as follows: "Since the introduction of salvarsan therapy for neurosyphilis, paralysis of various cranial nerves are seen more frequently. This higher frequency is in part only apparent since more attention has been given of late to auditory and labyrinthine disorders. On the whole, however, it must be considered that salvarsan does activate old foci which without salvarsan therapy would perhaps have remained latent. Perhaps we are dealing in some instances with fresh infections of neurosyphilis, in other cases with a Herxheimer reaction."

In the treatment of secondary syphilis with arsphenamine, the phenomenon of the Jarisch-Herxheimer[47a] reaction is observed. This reaction as was originally described, was a local one—an accentuation, reddening and swelling of the macular and papular rashes occurring within twenty-four hours after the use of mercury. Its occurrence was later given as a further proof that salvarsan exerts a powerful, direct effect on the treponemata. Before the discovery of the Treponema pallidum, this circumstance was frequently used for diagnostic purposes (a diagnosis by the method of Ex nocentibus), in order to determine whether isolated skin lesions which were only just visible, might be pronounced roseola or not.

Ehrlich regards the Herxheimer reaction and similar phenomena observed in salvarsan therapy as an inadequate action of the injection. In his opinion, in such cases the parasites are not at once destroyed, but instead only irritated, and in this condition produce an increased quantity of toxins.

Neisser[48] is undecided in his opinion as to the cause of the Herxheimer reaction, whether it is due to destruction of the treponemata and a consequent setting free of endotoxins, or, whether there is some kind of stimulus imparted to these organisms, with a resultant more copious secretion of toxic matter. Besides this "local" reaction, Neisser mentions a "general" one after treatment with arsphenamine, which is characterized by transitory increase of the headache in cerebral syphilis, and of the lightning pains in tabes.

At the present time the term "Herxheimer reaction" is used in a still more general way than Neisser's "general" reaction. It is given as the explanation of the "provocative" Wassermann reaction. It is used to explain local reactions other than in the original sense, for instance, a rupture of an aneurysm following the administration of salvarsan or acute yellow atrophy of the liver subsequent to jaundice and arsphenamine therapy.

The controversy regarding neurorecidive and the effect of arsphenamine upon the nervous system was started when Finger reported 9 per cent neurorecidive appearing in the course of treatment of five hundred syphilitics (mostly secondary cases) with arsphenamine. He stated, that during the same period he encountered only five cases of neurorecidive among two thousand patients treated with mercury and potassium iodide alone; that he had as many cases of neurorecidive among his five hundred salvarsan patients as Mauriac encountered among ten thousand syphilitics in the course of thirty years. Finger[49] regarded neurorecidive as due to the action of arsenic upon the nervous system. This contention was repudiated by Benario[50] who published a monograph on the subject in which he made an analysis of 116 cases. This writer pointed out "that the phenomenon of neurorecidive is syphilitic in nature and disappears as the result of treatment; that it occurs following treatment with mercury;* that its occurrence to the extent of 94 per cent was in the early period of syphilis (within 4 months after the administration of arsphenamine, 40 per cent occurred in the second month); that it did not occur in the presence of preexisting syphilitic disease of the nervous system."

The incidence of neurorecidive is variably quoted, the largest percentage being that of Finger. The occurrence of neurorecidive was considerably more frequent in the earlier period of arsphenamine therapy than it is at present. This can be explained on the basis of the treatment in vogue at that time, which was to administer one or two massive doses of arsphenamine in accordance with Ehrlich's unfulfilled dream of therapia sterilisans magna. Such treatment we now know in the light of experimental and clinical observations is potent of harm, for in addition to other reasons, it increases the likelihood of neurorecidive. Therefore, the incidence of neurorecidive is directly related to the method of treating acute cases of syphilis in vogue at different periods in the past, or, that practiced in different localities.

DISCUSSION OF OBSERVATIONS

The provoking of a spinal fluid by arsphenamine therapy from negative to positive-pleocytosis, the presence of globulin and a positive Wassermann reaction, which manifest an involvement of the nervous system is in all probability an expression of a Herxheimer reaction. Likewise, a neurorecidive is in all probability a clinical expression of this same reaction. In the first instance one can appropriately speak of this phenomenon as: "Neurosyphilis provocativa asymptomatica," and, in the second instance, as, "Neurosyphilis provocativa symptomatica.'' This explanation of a neurorecidive is on one hand a laboratory expression, and on the other hand a clinical expression of a Herxheimer reaction as substantiated by the following:

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*Mercury is less powerfully treponemicidal in action than is arsphenamine and is therefore less likely to produce a Herxheimer reaction. This reaction after the use of mercury occurs more frequently following those methods of administration in which the drug exerts its most powerful treponemicidal action. These methods are by inhalation and by inunction.

1. The considerations of Benario concerning neurorecidive.

2. The appearance of Treponema pallidum in otherwise normal spinal fluids.

3. The generally accepted view that the Herxheimer reaction is the explanation of the provocative Wassermann reaction.

The view expressed in the beginning of this paper that the nervous system of all syphilitics in the period of an acute treponememia is in all probability invaded by the parasite, and that the nervous system apparently in some cases does not react to this invasion, is not inconsistent with the view now expressed that the Herxheimer reaction is the cause of what is styled neurosyphilis provocativa asymptomatica and symptomatica. The arsphenamine most likely causes a reaction of the nervous system to the presence of treponema. We know that arsphenamine is capable of causing such reaction on the part of certain tissues to treponema which prior to the use of this drug showed at least no macroscopic reaction. For instance, the local Herxheimer reaction which occurs during the eruptive stage is often noted in areas where no gross lesions could previously be demonstrated. Moreover, from the classical work of Warthin[51] we know that there exists an apparent symbiosis of the tissues with treponemata, and that in some instances such tissues show no reaction to the parasite.

We did not observe the provocative spinal fluid change in all cases studied, but we did not vary the time of examination. In the second observation reported (page 568) there occurred a provocative spinal fluid change, but without clinical manifestation of a nervous system involvement. Whether all such cases eventually develop clinical manifestations can not at this time be answered. However, Ravaut has pointed out that changes in the spinal fluid could precede clinical manifestation a long time. He also showed, however, that the spinal fluid could again become normal without clinical symptoms.

The occurrence of neurosyphilis following the administration of arsphenamine in Case No. 11 probably supports the belief that it is possible with the improper use of arsphenamine in the treatment of tertiary syphilitics, to provoke neurosyphilis as manifested in either the asymptomatic or symptomatic stage. As has been already pointed out, the reaction on the part of syphilized tissues in the late period of the disease to the presence of treponema would constitute an allergic phenomenon. Therefore the following explanation should be considered: that the intensive treatment with arsphenamine may have activated latent neurosyphilis in this individual. This explanation in the light of clinical observations and knowledge concerning neurorecidive, Herxheimer reaction, and the phenomenon of allergy, is the more likely one.

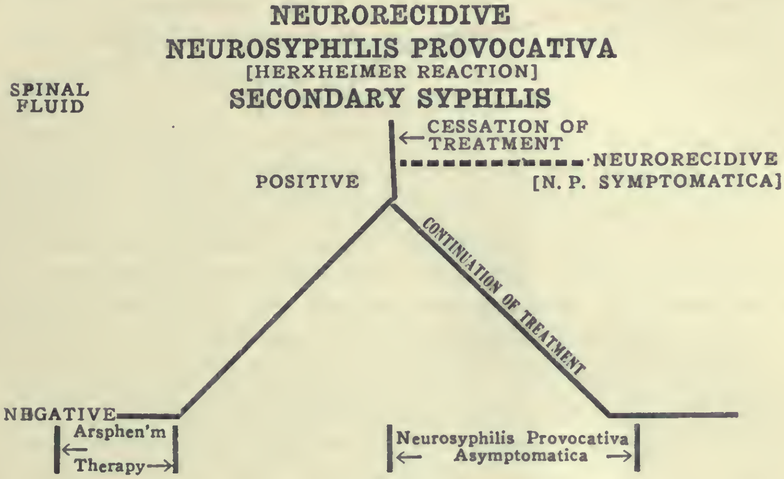
NEURORECIDIVE
NEUROSYPHILIS PROVOCATIVA
[HERXHEIMER REACTION]
SECONDARY SYPHILIS
SPINAL FLUID
CESSATION OF TREATMENT
NEURORECIDIVE [N. P. SYMPTOMATICA]
POSITIVE
CONTINUATION OF TREATMENT
NEGATIVE
Arsphen'm Therapy
Neurosyphilis Provocativa Asymptomatica

Fig. 1.

Figure 1 is a graphic representation of the observations herein reported. As already pointed out neurorecidive is regarded as an expression of a Herxheimer reaction and may be spoken of as neurosyphilis provocativa which latter is divided into two stages, the laboratory or asymptomatic stage, and the clinical or symptomatic stage. This latter stage is ordinarily spoken of as neurorecidive. The spinal fluid at first negative, may after arsphenamine therapy become positive-lymphocytosis and the presence of globulin—the "meningo-recidives histologique" of Ravaut. In the absence of clinical evidence of a neuraxis involvement this stage is the asymptomatic stage as illustrated in observation No. 2 herein reported. From our other observations, those of Altman and Dreyfus, Ravaut, and from clinical observation we can conclude that after provocative spinal fluid changes have been produced that one of two possibilities exists,—the cases progress, which is more likely after the cessation of treatment, into a clinical expression of neurosyphilis, the symptomatic stage, or the "provocative neurorecidive" of Altman and Dreyfus. The other possibility is the occurrence of a negative spinal fluid spontaneously, or, as the result of treatment, and it may be stated here that Nonne mentions with no little emphasis the occurrence of spontaneously cured or abortive forms of neurosyphilis.

The Herxheimer reaction may be called an expression of the "heavy artillery" action of arsphenamine, and from this view is a vicious reaction. Its presence is prognostically of bad significance. It should therefore be avoided in the arsphenamine therapy of syphilis. Neurorecidive, a clinical expression of this reaction, is the bugbear in the arsphenamine therapy of early syphilis. In one's clinical experience neurorecidive is not rare, particularly if routine neurologic and spinal fluid examinations are made of all syphilitic patients. Following this custom I have noted in late secondary cases minor neurologic abnormalities, a history of headache which appeared a short time after the last of a few injections of arsphenamine administered during the acute stage of the disease and then the cessation of all treatment. Such instances are represented in Cases 9 and 10. If the view that this type of case is an instance of neurorecidive is correct (and it is founded upon the history of headache appearing after the use of arsphenamine, together with our knowledge that such treatment increases the likelihood of neurorecidive), then in my experience neurorecidive is not by any means infrequent. On the other hand, if one considers neurorecidive only as the frank occurrence of one or the other types of neurosyphilis appearing after salvarsan administration, then its occurrence is much less frequent.

There is apparently an increasing tendency to treat syphilis exclusively with arsphenamine. This is probably not the most rational method of treatment for all periods of syphilis, and particularly for the stage of the acute treponemenia. The most rational treatment of the disease at this period is one which will minimize the possibility of the occurrence of a neurorecidive, namely the thorough and sufficient administration of mercury preceding the use of arsphenamine. Indeed, Altman and Dreyfus recommend two weeks' inunctions with mercury at this time before starting the use of arsphenamine. Gennerich advocates the administration of 4 to 6 intramuscular injections of calomel before the use of arsphenamine in secondary syphilis. The use of small doses of this drug, certainly, at least for the first few injections, and then the persistent administration of the drug in courses rather than the haphazard "now and then" method is to be preferred.

The incidence of neurorecidive has led to the statement that neurosyphilis has been increased since the use of arsphenamine as a therapeutic agent in the treatment of syphilis. The notable champion of this view was the late Gaucher. In a sense this accusation is true, but it is based upon the improper use of the drug as a therapeutic agent.

REPORT OF CASES

Early Neurosyphilis Asymptomatica

Case 1.—Male, age 28. A painter by occupation. Uses alcohol moderately. Family history, nothing remarkable. A history of an initial genital lesion five months ago. Local treatment applied, which healed the sore. Four months later another genital lesion which received only local treatment. No history of past or present headache. His only subjective complaint is "nervousness," although he can not tangibly define this complaint. He is what is generally known as a "nervous" type of patient, that is, he is apprehensive, easily irritated and anxious. He states that he has always been of a "nervous" type and does not think this "nervousness" has been worse since his infection with syphilis.

Clinical.—A tall, sharp featured, visceroptotic type. General physical examination is negative. The only evidence of a syphilitic infection is a generalized adenopathy. Heart action is normal. Auscultation at the base of the heart is negative.

Neurologic.—Emotional tone is one of apprehension. The pupils are negative. All reflexes are normal. Station is normal. No sensory disturbances. Eyeground examination is negative. Tuning fork test of eighth nerve is negative.*

Wassermann of the Serum, 4-plus.

Spinal Fluid: 120 lymphocytes per c.mm. One-plus. Globulin.

Wassermann: 1 c.c.—4-plus (cholesterolized antigen).
.5 c.c.—4-plus.
.4 c.c.—4-plus.
.3 c.c.—4-plus.
.2 c.c.—3-plus. Gold Sol 1222000000.

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*The Wassermann reaction in these case history reports was performed with a cholesterolized antigen, unless otherwise stated. The test for globulin was made with Noguchi's Butyric Acid Test.

The following standard of Swift was used in reading the reaction:
− ....Opalescence to very faint haze.
+ − ....Faint haze to haze.
+ ....Fine granular precipitate.
+ + ...Heavy granular or coarse flocculent precipitate.
+ + + ...Very heavy flocculent precipitate.

With an alcoholic antigen the reaction was the same except with .2 c.c. of spinal fluid a 2-plus was obtained and was negative with .1 c.c.

Case 2.—Male, age 23. Denies the use of alcohol. A history of a genital lesion about two months ago. Received only local treatment which healed the sore. About two weeks ago an eruption appeared on the body. No subjective complaint suggestive of early neurosyphilis.

Clinical.—Well developed and nourished. General physical examination is negative except an indurated scar at the site of former sore, a macular papular syphilide on trunk, arms and legs, mucous patches on lips, tongue, and tonsils, and a generalized adenopathy.

Neurologic.—Emotional tone is normal. The pupils are negative. All reflexes are normal. Station is normal. No sensory disturbances. Eyegrounds are normal. Tuning fork test of eighth nerve is negative.

Serum Wassermann.—4-plus.
Spinal Fluid.—54 lymphocytes per c.mm.
1 plus Globulin.
Gold Sol. 0011100000.
Wassermann.—2 c.c.—4-plus.
1 c.c.—Negative.

Early Neurosyphilis Symptomatica

Meningeal Type—Severe Headache

Case 3.—Male, age 31. A history of genital sore, about two months' duration, treated locally. Eruption appeared about two weeks ago, since which time he has been taking mercury pills. For the past two or three weeks he has complained of severe constant headache, tinnitus, vertigo, malaise and anorexia.

Clinical.—Indurated remains of chancre in sulcus, generalized adenopathy, large papular syphilide, diffuse on trunk, limbs and face. General physical examination otherwise is negative.

Neurologic.—Emotional tone is normal. Pupils are negative. Station, slight swaying. Patella reflexes are exaggerated. Eyegrounds: an optic neuritis. Eighth nerve, positive tuning fork test.

Serum Wassermann.—4 plus.
Spinal Fluid.—Refused puncture.

Diffuse Meningeal Type—Simulating Epidemic Type of Cerebrospinal Meningitis

Case 4.—Male, age 26. Denies ever having had a genital sore. For the past ten days he complained of severe headache of increasing severity, fever, vomiting and ringing in the ears. About two to three days prior to admission he became delirious. At this time his condition was regarded as acute cerebrospinal meningitis, epidemic type.

Condition on Admission.—He was confused, disoriented, incoherent and irrelevant, not completely accessible or cooperative.

Clinical—Emaciated, no apparent focus of an infection. Heart and lungs are negative. The only possible stigmata of syphilitic infection is a fissured and furrowed tongue. This is either syphilitic in nature or a so-called scrotal tongue.

Neurologic.—The pupils are unequal, react very sluggishly to light. Patellar reflexes are exaggerated and unequal. A bilateral paresis of the 6th nerve, other ocular muscles are normal. The 5th and 7th nerves are normal, the eighth nerve not tested. Slight Kernig's sign. Rigidity of neck. Eyegrounds are negative.

Fields of vision roughly normal.

Serum Wassermann.—4-plus (Three different tests).

Spinal Fluid.—Smear and culture, negative. Cells, 215.

Globulin, 3-plus.

Gold Sol. 0012210000.

Wassermann.—2 c.c.—4-plus.
1 c.c.—4-plus.
.5 c.c.—2-plus.

After antisyphilitic treatment there was an immediate and continued clinical improvement.

Diffuse Meningeal Type—Acute Psychosis

CASE 5.—Male, age 37. A German ex-naval petty officer. A history of a chancre about three years ago. Was treated intensively with arsphenamine in Generich's service at the Naval Hospital at Kiel. Cessation of all treatment. During almost the entire duration of the War has been on submarine duty in the North Sea. No subjective recurrence of syphilis or subjective symptoms of neurosyphilis. After the cessation of the War has been a petty officer on one of the German merchant marine vessels loaned to the United States Government. While acting in this capacity during one of the voyages to this country, he developed an acute psychosis. He acted and spoke "queerly." Attempted to stop the vessel to go swimming, became disrespectful to superior officers, attempted to set fire to the vessel, became maniacal.

Condition on Admission.—He was much excited, confused, disoriented, incoherent, not accessible or cooperative. This excited state was of very short duration, for in a few days his psychomotor activity became more normal, and he was then oriented, coherent, accessible and cooperative, but was humoristic, slightly euphoric, playful, a wide range of thought processes. In about one week (no antisyphilitic treatment was administered), his emotional tone was normal, no delusions or hallucinations, insight present, no memory or speech defect. He denied ever having had a similar attack.

Clinical.—The only noteworthy clinical findings were:—scar on glans, general adenopathy.

Neurologic.—Pupils equal, react sluggishly to light, brisk patella reflexes, eyeground examination disclosed an optic neuritis.

Serum Wassermann.—4-plus.

Spinal Fluid.—Small lymphocytes, 231. Large lymphocytes, 11. Plasma cells, 2. Polys, 4. Endo., 7. Globulin, 2-plus.

Gold Sol.—5555543300.

Wassermann.—1 c.c.—4-plus.
.8 c.c.—4-plus.

The spinal fluid was negative for Treponema pallidum by the following technic. The entire coagulum produced by the addition of 95 per cent alcohol in 15 c.c. of spinal fluid was stained with Fontana's stain.

Paretic Type

Case 6.—Male, age 34. Medical student. History of a genital lesion three years ago (no previous lesion) which appeared three weeks after exposure. No treatment until the appearance of the secondary eruption six weeks later. Received weekly intramuscular injections of mercury for the following year. One injection of arsphenamine which was administered six months after the eruption. About the time of infection he matriculated as a medical student and attended college from 9 A.M. until 5 P.M.; in addition he worked as a postoffice clerk from midnight until 8 A.M. He did this for two years until he experienced a ''nervous breakdown.'' The onset of the ''nervous breakdown'' was about eighteen months ago when he became irritable, easily lost his temper, lacked concentration, became forgetful, fatigue easily induced, insomnia, periods of depression and lacked emotional control.

Present Condition.—General physical examination discloses nothing of any importance. No general evidences of syphilitic infection. Mental examination.—Emotional tone is one of agitation. He has insight and recognizes his condition as due to syphilis. At times his emotional tone is variable, he cries very easily. Decreased cerebration. Some memory defect. No delusions or hallucinations.

Neurologic.—Pupils are normal. Reflexes are normal excepting the knee jerks are lively. Speech defect. Slight tremor of tongue and hands.

Serum Wassermann.—4-plus.

Spinal Fluid.—Cells, 8 lymphocytes. Globulin, 2-plus.

Gold Sol, 5554332100.

Wassermann.—1 c.c.—4-plus.
.7 c.c.—4-plus.
.5 c.c.—4-plus.
.3 c.c.—4-plus.

Meningeal Vascular Type—Epileptiform Seizure

Case 7.—Male, age 23. A history of a chancre eighteen months ago followed by a secondary eruption. In the primary stage a liquid medicine (mercury?) was administered. At the appearance of the eruption arsphenamine was first administered and consisted of a total of seven intravenous injections, and two intramuscular injections of mercury. Cessation of all treatment. No complaint until one year later. At this time he complained of headache and experienced an attack of unconsciousness, speech and memory disturbances. This time the serum Wassermann was 4-plus; the spinal fluid was not examined. He received a total of eight intravenous injections of arsphenamine and six intramuscular injections of mercury. He has had no complaint until about one month ago, at which time was the onset of his present complaint of headache.

Clinical.—General physical examination is negative excepting scar on penis, general adenopathy, sharply marginated infiltration and congestion of the soft palate suggestive of a beginning gumma.

Neurologic.—No paralysis. Pupils are equal and react normally.

Station.—Slight swaying. Exaggeration of the left biceps, triceps, patella and tendo-Achilles reflexes. Speech disturbance to the conventional test phases. No memory defect. No tremors. Emotional tone is normal.

Serum Wassermann.—4-plus (cholesterolized and alcoholic antigen).

Spinal Fluid.—134 lymphocytes. Globulin, 2-plus.

Gold Sol, 5555554000.

Wassermann (Cholesterolized and Alcoholic Antigen).—
1 c.c.—4-plus.
.5 c.c.—4-plus.
.3 c.c.—4-plus.

Parenchymatous Type—Transverse Myelitis

Case 8.—Male, age 27. Chauffeur by occupation. Excessive user of alcohol. Married seven months ago. An ulcerative and destructive genital sore (no previous one) six months ago, following extramarital intercourse. Local treatment applied which healed the sore in about one month. In addition he received about five intramuscular injections of mercury, and for one month mercury by mouth. Denies secondary eruption. No subjective complaint until six months later at which time he complained of pain (not severe) across the lumbar region and paresthesia of both legs, followed by increasing weakness in both legs; three days later he developed complete paralysis of both lower limbs with loss of sphincter control. No history of trauma or recent infectious disease.

Clinical.—No evidence of a systemic infection. Heart and lungs are negative. Extensive scar on glans penis, general adenopathy.

Neurologio.—Pupils are negative. Paralysis of lower extremities, loss of all reflexes, loss of sensation from level of anterior iliac spines, incontinence of both sphincters. Eyegrounds are negative. Eighth nerve not tested.

Serum Wassermann.—4-plus.

Spinal Fluid.—262 cells per c.mm. Globulin, Nonne, 2-plus. Noguchi, 2-plus.

Gold Sol, not tested.

Wassermann.—1.5 c.c.—4-plus.
1 c.c.—4-plus.
.5 c.c.—4-plus.

Developed extensive bed sores. Death resulted three months from the onset of paralysis. Autopsy not obtained.

Examination of Spouse.—Age, 24. Mucous patches both tonsils. Acute laryngitis. Pigmentary remains of a recent eruption on body. Leucoderma on neck, general adenopathy. No subjective or objective evidence of neurosyphilis.

Serum Wassermann.—4-plus.

Refused spinal puncture.

Neurosyphilis Provocativa Symptomatica—Early Type

Case 9.—Male, age 29. Uses alcohol moderately. A history of a genital lesion ten months ago which was treated only locally. Two months later throat became sore. At this time he was given four consecutive intravenous injections of arsphenamine (dose unknown to patient). No other treatment. About two to three months after this treatment he complained of headache. The Wassermann reaction then was 4-plus (spinal fluid not tested). He again received two intravenous injections of arsphenamine and four intramuscular injections of mercury. No further complaint.

Clinical.—The noteworthy clinical findings are the following: Mucous patch, right tonsil; general adenopathy; scar on penis.

Neurologic.—Emotional tone is one of anxiety. The only neurologic abnormalities are lively patella reflexes and an optic neuritis.

Serum Wasserman.—4-plus.

Spinal Fluid.—22 lymphocytes per c.mm.
2-plus globulin.
Gold Sol, 1224320000.

Wassermann (both with cholesterinized and alcohol antigen).—
1 c.c.—4-plus.
.5 c.c.—4-plus.
.2 c.c.—Negative.

CASE 10.—Male, age 25. Alcohol very moderately. A history of a genital sore six months ago. The following treatment was administered:—Four injections of arsphenamine (dose unknown), at two day intervals, and one intramuscular injection of mercury. The duration of the chancre at the time of this treatment is not definitely known to the patient, but at this time the Wassermann was four-plus. No subjective complaint of neurosyphilis at this time. Cessation of all treatment. At present, the only complaint is headache, duration two to three months.

Clinical.—Pigmentation at site of chancre, generalized adenopathy. Pigmentary remains of secondary eruption, mucous patches. General physical examination otherwise was negative.

Neurologic.—The only possible neurologic abnormality was lively patella reflexes.

Serum Wassermann.—4-plus (alcoholic and cholesterolized antigens).

Spinal Fluid.—17 lymphocytes. Globulin, 2-plus.

Gold Sol, 1123220000.

Wassermann.—2 c.c.—4-plus.
1 c.c.—4-plus.
.5 c.c.—4-plus.
.4 c.c.—4-plus.
.3 c.c.—3-plus.
.2 c.c.—Negative.

Late Type

CASE 11.—Male, age 30. A moderate user of alcohol. A history of a genital sore four years ago. Received local treatment and internal administration of "pills" for about three months. No history of an eruption. All treatment ceased and he was free of all symptoms. Three years later, at which time he was in the army, a routine Wassermann was made which was 4-plus. He then received intensive treatment. Intramuscular injections of mercury and intravenous injections of arsphenamine (dose unknown to patient) at intervals which he recalled were about three, five, and seven days. About six months from the beginning of this treatment he developed severe headache, vertigo, a period of confusion, an attack of unconsciousness (epileptiform seizure) and a right facial paralysis. Spinal fluid examination was made, result unknown to patient. Improvement under treatment.

Clinical.—The noteworthy clinical findings are the following: Scar on glans penis, bullet type general adenopathy.

Neurologic.—Emotional tone is normal. No memory or speech defect. Paresis of the right side of the face. Pupils are negative. Station is normal. Biceps and triceps reflexes are normal. The right patella and Achilles tendon reflexes are exaggerated; those on the left side are normal. No ankle clonus. Suggestive Babinski on the right side.

Serum Wassermann.—4-plus.

Spinal Fluid.—50 lymphocytes per c.mm. Globulin, 2-plus.

Gold Sol, 4443331000.

Wassermann.—2 c.c.—4-plus.
2 c.c.—4-plus.

Certain Laboratory Aspects in the Spinal Fluid in the Early Period of Syphilis

Case 12.—Male, age 26. A genital lesion about six weeks ago. Phimosis rapidly developed. Local treatment only. Eruption on body 3 days' duration. No subjective symptoms of neurosyphilis.

Clinical.—Partly adherent foreskin, chancre in sulcus, (dark-field positive), maculo-papular eruption on body. Generalized adenopathy. Cardiac rate 130 at rest, 160 after exercise, fine tremor of hands, probably N. C. A. (Neurocirculatory asthenia).

Neurologic.—No objective evidence of neurosyphilis.

Serum Wassermann.—5th day of chancre, negative; 10th day, negative; between 5th and 6th week, 4-plus.

Spinal Fluid.—2 lymphocytes per c.mm. Globulin, negative.

Gold Sol, 0011100000.

Wassermann, with an alcoholic antigen.—1 c.c.—Negative.
.5 c.c.—Negative.
.2 c.c.—Negative.

With a cholesterinized antigen.—1 c.c.—4-plus.
.5 c.c.—Negative.
.2 c.c.—Negative.

Case 13.—Male, age 28. A genital lesion about six weeks ago, local treatment only. Eruption on body about 10 days' duration. No subjective complaint of neurosyphilis.

Clinical.—Concealed chancre, beneath a phimosed foreskin, generalized adenopathy. Maculo-papular eruption on body. Cardiac rate of 120, otherwise cardiac examination is negative.

Neurologic.—No neurologic abnormalities.

Serum Wassermann.—4-plus.

Spinal Fluid (examined 3 days after an injection of .2 gm. of arsphenamine and one intramuscular injection of mercury salicylate gr 1½).—4 lymphocytes.

Globulin, plus-minus.
Gold Sol, 1122110000.
Wassermann.—1 c.c. Negative.

DISCUSSION OF CASES

Instances of early neurosyphilis asymptomatica are represented in Cases 1 and 2. In both cases, one an individual in the eruptive stage, the other in the fifth month of his infection, subjective as well as objective symptoms of a nervous system involvement were absent. The spinal fluid in each case presented definite laboratory evidences of an involvement of the neuraxis.

It is of interest to note that Case 1 complained of so-called "nervousness." It is doubtful whether any relationship existed between this symptom and his infection with syphilis. The relationship between syphilis and the psychoneurotic group of symptoms has not been clearly defined. In this regard one may appropriately recall Kroeplin's syphilitic neurasthenia in his classification of the syphilitic psychoses. In a way these cases are instances of the type which Southard and Solomon[52] have termed "paresis sine paresia."

Our knowledge is not complete as to the outcome of this type of neurosyphilis if untreated or insufficiently treated. However, we know that the asymptomatic stage of neurosyphilis may precede for a long time the symptomatic stage. Or, the process may become spontaneously cured, or it may remain latent. This type of neurosyphilitic probably represents that class of syphilitic, which we know exists from clinical observations, who after experiencing traumatic or psychic shock acutely develops clinical symptoms of neurosyphilis. We also know from clinical experience that it is possible to activate latent neurosyphilitics by improper treatment with arsphenamine.

One hope in the combating of neurosyphilis lies in the diagnosis and treatment of the disease in the asymptomatic stage rather than in the symptomatic stage of intellectual deterioration.

Although the spinal fluid was not examined in Case 3, yet the clinical evidence leaves no doubt as to an involvement of the nervous system.

In Case 4, although there was a denial of infection, yet this diffuse meningeal type of neurosyphilis is seen only comparatively early in syphilis; the case is, therefore, placed in the early group of cases.

In Case 5 there were some aspects which suggested maniac type of maniac depressive insanity. However, this diagnosis can be excluded by the fact that this psychosis was the initial attack appearing at the age of 37, the short duration of the psychosis and by neurologic and laboratory findings. The diagnosis of paresis should also be considered. However, the spontaneous remission in such a short time, the paucity of neurologic and psychiatric findings would tend, but not necessarily, to exclude paresis as the correct diagnosis. This diagnosis is suggested by the type of curve in the gold sol and by the finding of plasma cells in the spinal fluid. However, these laboratory findings are not infallible signs of paresis. In all probability the correct diagnosis is a diffuse meningeal type of cerebrospinal syphilis.

Case 6 is a remarkable instance of what is most likely early symptoms of paresis appearing eighteen months after infection. These symptoms are rather characteristic of one type of early symptoms of paresis. However, this case may be one of cerebrospinal syphilis, since differentiation from paresis in the early period is difficult.

From the history and the neurologic findings in Case 7, one can conclude that the patient experienced a transient hemiplegia about one year after infection. It is important to note that there are some clinical and laboratory features suggestive of paresis. However, this diagnosis can not be substantiated by these findings.

Case 8 is a remarkable instance of transverse myelitis of syphilitic origin occurring six months after infection. The clinical findings of secondary syphilis on the spouse (whom he had recently married) substantiate the history of a recent infection. The prodromal symptoms present are rather characteristic of this type of neurosyphilis.

The spinal fluid findings in Cases 12 and 13 are representative of a class of early syphilitics who present no subjective or objective evidence of neurosyphilis. These findings are very slight changes in the gold sol (some or all of the first tubes show changes rarely exceeding 3) and the Wassermann may be positive only in the higher amount (1 c.c. or more). The significance of these slight changes in the gold sol as evidencing an alteration in the spinal fluid can not be definitely stated. The sensitiveness of the gold sol solution and the personal equation in the reading of such curves are factors which should be considered. These slight changes may be obtained in supposedly normal fluids. They are, however, perhaps more frequently observed in my experience in the spinal fluid in the early period of syphilis. It is to be noted that in some of the other cases reported very slight changes occurred in the first five tubes of the gold sol, yet, from the other spinal fluid findings there was no doubt as to an involvement of the nervous system. In the reports of early spinal fluid changes in syphilis quoted in the beginning of this paper, the report of the gold sol findings are lacking in most instances. However, the report of Smith and Dennie is an exception. These writers report similar slight changes in the gold sol in which the spinal fluid abnormalities were present as well as absent. It is possible that the gold sol is the most sensitive indicator of a neuraxis involvement in the early period of syphilis. If such is the case all fluids showing changes in the gold sol curve would place the case in the meningo-recidive histologique group of Ravaut.

The interpretation of a positive Wasserman reaction (which not infrequently occurs only in the higher amounts of spinal fluid used) as an isolated laboratory finding in the spinal fluid, is suggested by the work of Kolmer and Sekiguchi.[53] These investigators were able to obtain a positive Wassermann reaction in the spinal fluid of dogs after injecting them intravenously with human syphilitic serum. Kolmer and Sekiguchi point out that their findings suggest an infiltration of syphilitic reagin from the blood into the spinal fluid, and in all probability explain the occurrence of a positive Wassermann in the spinal fluid in the absence of other spinal fluid abnormalities, rather than due to an invasion of the nervous system with treponemata and a reaction on the part of the nervous system to their presence.

SUMMARY

It is apparent from clinical and laboratory evidences that there is an involvement of the nervous system in a large group of cases in the early period of syphilis. In addition to this group there is another, without neurologic or spinal fluid abnormalities other than the presence of the treponema in the fluid. These observations together with our clinical and laboratory knowledge concerning the invasive powers of the treponema during the period of acute treponememia support the belief expressed, that at this time probably in all cases of syphilis, the nervous system is invaded by the parasite. The nervous system at the time of the invasion may or may not react to the organism.

The clinical phases of early neurosyphilis are presented. The early neuraxis involvement may be meningeal, vascular or parenchymatous. The meningeal type is the most frequent and is divided into four clinical groups. One of these groups—the asymptomatic, in which there are conspicuous spinal fluid changes indicative of a meningeal involvement is particularly pointed out.

Of the cranial nerves the eighth is the most frequently involved, then in order of frequency are the following: The second, seventh, third, fourth, fifth and sixth.

Observations are recorded in which positive spinal fluid changes were noted after arsphenamine therapy in previously untreated cases of secondary syphilis with negative spinal fluids. In one case there were only spinal fluid changes, in another, in addition, there was clinical evidence of neurosyphilis. In the latter instance this phenomenon is ordinarily known as neurorecidive. A brief review of the literature is made concerning the observations of others on this subject. Neurorecidive and the Herxheimer reaction are defined and a brief review of the literature is made. Observations are presented in substantiation of the view expressed that neurorecidive is an expression of a Herxheimer reaction. This phenomenon-neurorecidive, is divided into two stages, the laboratory or asymptomatic; the clinical or symptomatic. The former is styled: "neurosyphilis provocativa asymptomatica," the latter, "neurosyphilis provocativa symptomatica."

The Herxheimer reaction is regarded prognostically of bad significance and its excitation should, therefore, be avoided in the treatment of syphilis.

The harmfulness of the insufficient and exclusive use of arsphenamine in the early treatment of syphilis is pointed out.

Case-histories of early and late secondary syphilis are presented which show various clinical and laboratory aspects of early neurosyphilis.

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CONGENITAL SYPHILIS IN ORTHOPEDIC CLINICS

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TO those who are familiar with the widespread dissemination of syphilis through hereditary channels, and with the bizarre and almost limitless clinical expressions of this type of lues, it will appear perfectly natural that orthopedic clinics should yield a very considerable variety of cases whose origin might be traced back to an ancestral infection. As a matter of fact, however, the influence of syphilis in orthopedic work is not generally recognized. We have been content to ascribe to inherited syphilis certain conventional lesions such as osteochondritis of infancy, osteoperiostitis, dactylitis and certain forms of arthritis appearing in children, and to say, as one well known author has put it, that inherited syphilis may affect the bones of the spine and large joints causing local deformity and symptoms that can not be distinguished from tuberculous lesions, ''but as compared with tuberculosis, it is a rare disease.''

In the course of investigations carried on during the past few years in the clinics of the Post Graduate and Mount Sinai Hospitals and the Hospital for Ruptured and Crippled I have treated several hundred cases of various kinds whose response to mercury and potassium iodide leads to the belief that inherited syphilis has been an important factor in their etiology if not entirely responsible for the disabilities presented. It was not possible in the pressure of clinic work to record all of these cases, but data on a sufficient number has been preserved to establish the fact that mercury and potassium iodide are frequently more effective than surgery or mechanical appliances in the treatment of certain orthopedic conditions. Or, to state the case more correctly, general recognitioin of the prevalence of inherited syphilis and its potency in producing disabilities of function would often eliminate the necessity for surgical or mechanical treatment.

This series of cases includes 81 joint conditions simulating tuberculosis; 14 cases of osteomyelitis of the long bones; 5 cases of torticollis; 12 simple myotonias; 5 cases of adenitis supposed to have been tuberculous; 17 cases of myositis some of which presented symptoms usually attributed to sacroiliac strain; 24 cases of arthritis; 8 cases of disease of the carpus or tarsus; 16 cases of chronic headaches; 10 cases of osteochondritis of the hip; one case of lateral curvature; 33 cases of caries of the spine; and one case of lymphangitis; a total of 226 cases.

To say that all of these are syphilis would be to advance a contention beyond the realm of proof. It can be said, however, that they all presented some evidence of an inherited taint and that they all responded to antisyphilitic therapy. This leaves us with the choice of one of two conclusions. Either syphilis was a factor in the production of these disorders or else in mercury and potassium iodide we have two remedies whose efficacy has not been fully appreciated.

The difficulty of proving ancestral infection in clinic patients is obvious. It is a hopeless task to endeavor to elicit the medical histories of grandparents, aunts and uncles, and frequently impossible to determine the presence of syphilis in the parents themselves, for it is seldom that both can be reached for examination. The procedure adopted, therefore, was to subject suspected cases to antiluetic treatment and the end seems to have justified the means.

Wassermann tests were made in 47 of the bone and joint cases with varying results. With alcoholic extract of heart there were 11 weak positives and 36 negatives. The same bloods tested with cholesterinized antigens gave 33 positives from one-plus to four-plus, and 14 negatives. Negative reactions occurred where the family history was positive and the lesions cleared up on the administration of mercury and potassium iodide, a finding which serologists of experience have reported as extremely frequent in cases of inherited syphilis where clinical manifestations do not appear for some years after birth. In view of this and of the somewhat difficult conditions under which this study was made, blood tests were often omitted.

Perhaps the most interesting results were those obtained in lesions of the spine and large joints where the symptoms were identical with those produced by tuberculosis, and in many of which a diagnosis of tuberculous disease had been made by competent orthopedic surgeons and the patients treated on that theory from one to ten years by the usual methods of immobilization. There were 114 of these who showed perceptible improvement in from two to three weeks and most of the cases where the large articulations were involved became symptom free in from two to six months. The word cure is inadmissible at this period of treatment. In the writer's opinion it is hardly safe, from a therapeutic standpoint, to consider that inherited syphilis differs fundamentally from the acquired type. If from clinical manifestations it can be argued that in many cases the virulence of the spirochetes is somewhat modified, still there is no certainty that their resistance to drug influence has been materially altered. In a number of instances where the patients had become symptom free and medication was stopped too soon relapses occurred. On the resumption of proper therapy, symptoms in these cases again rapidly subsided. The conclusion seems reasonable that the path of safety lies in continuing treatment at least a year after all evidence of active disease has ceased.

This study appears to have demonstrated that chronic articular lesions due to invasion by either tubercle bacilli or Treponema pallida produce the same clinical picture. The syndrome on which a diagnosis of tuberculous joint disease has heretofore been based merely indicates the presence of a chronic destructive process without offering a clue to its etiology. Therapeutic measures afford a means of determining the probable presence of syphilis, and it is the writer's belief that to pronounce a diagnosis of joint tuberculosis without first eliminating the possibility of inherited syphilis by at least five or six weeks of vigorous antiluetic treatment is to jeopardize the welfare of the patient and to unjustly condemn to permanent disability joints whose functional efficiency might have been preserved.

Among the other conditions approached on the theory that inherited lues probably accounted for the lesions were 14 cases of osteomyelitis. One of these, in which the tibia was involved, had been operated four times during a period of six years and the process had again become active with one discharging sinus. All symptoms disappeared and the sinus healed after six weeks of mixed treatment. Two others showing radiologic evidence of considerable bone destruction were scheduled for operation, but cleared up entirely under the use of mercury and potassium iodide. In one of these, a tibia case, in which treatment was discontinued too early, a secondary lesion of large size appeared in the lower third of the radius and was controlled by proper medication. Another case involving the radius remained well for a year and subsequently broke down, mercury having been discontinued at the end of six months, and it again promptly yielded to proper treatment.

Five cases of torticollis were of peculiar interest. One, a girl of ten, had had her deformity since birth and was operated three times without correction. Marked hypoplasia of the enamel of the upper incisors indicated a syphilitic taint and she was placed on $\frac{1}{32}$ grain of bichloride of mercury and ten grains of potassium iodide three times a day. In six weeks the position of the head and functions of the neck were entirely normal. It was later discovered that her father had syphilis before marriage and that both father and child had positive Wassermanns. Two other cases of wry neck uncorrected by operation and one unoperated case were relieved by mixed treatment in less than a month. Muscle irritation by toxines, probably of syphilitic origin, were not very uncommon. Two striking cases, one in which there was a marked lateral curvature of the spine and the other with a rigid spine which was responsible for a diagnosis of Pott's disease, are among those recorded in which symptoms rapidly disappeared under antisyphilitic treatment. Four others showed tenderness of the glutei with symptoms which appeared to justify a diagnosis of sacro-iliac strain and responded promptly to the usual drugs.

The cases of extensive cervical adenitis were remarkable only because syphilis had not been considered as a probable cause. In these conditions, as in the joint disabilities of children, tuberculosis is too often blamed without reason. One adult had consulted well-known surgeons in various large cities, all of whom made a diagnosis of tuberculous glands because there was no history of acquired syphilis. The condition was controlled by mercury and potassium iodide and there was dental evidence and a family history suggestive of lues.

Chronic headaches were frequently encountered in both children and adults where there was dental evidence of syphilis and these all responded rather readily to treatment.

Several cases of multiple arthritis of long standing cleared up under mixed treatment. In all of them there was dental evidence of spirochetal infection.

The myotonias seen in children between the ages of four and ten yielded very quickly to treatment. Among the boys there were histories of inability to run and jump as well as other boys of the same age, of frequent tumbles, of instability in balancing, and of lack of interest in active games. In private cases of this nature it has usually been possible to obtain evidence of family taint and more than one mother has remarked on the rapid results obtained from the ''tonic'' the children were given. In several instances the mental quickening was quite as noticeable as the physical improvement.

The ten cases of osteochondritis of the hip, frequently spoken of as Perthes' disease, Legg's disease or ''quiet hip disease,'' yielded very strong evidence of the syphilitic origin of this form of hip disease whose etiology has been a subject of discussion since it was first described about ten years ago. Not only was there rapid recrudescence of acute symptoms, when they existed, but of eight bloods tested with cholesterinized antigens one gave a four-plus reaction, one a three-plus, two a two-plus and three a one-plus. In two the family history was positive. These facts, taken together with the character of the lesion, osteochondritis, which is a common expression of syphilis in the joints of younger children, would seem to indicate the probability that this malady is another of the varied disabilities for which inherited syphilis is responsible.

Reviewing this series of cases as a whole the conclusion is inevitable that many syphilitic infections which find their way into orthopedic clinics pass through unrecognized, first because the tradition that nearly all chronic destructive lesions of the spine and large joints are tuberculous has been accepted without question, and second, because the far-reaching distribution of congenital syphilis and its potential dangers have been ignored.

CHRONIC DIARRHEA PROBABLY DUE TO SYPHILIS

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THANKS largely to the Wassermann we are recognizing more frequently syphilitic disease of the internal viscera. The diagnosis of syphilis of the stomach is not so uncommon nowadays, but syphilis of the pancreas and intestine remain quite rare. The following case is therefore placed on record with the usual introductory apology—because of its exceeding infrequency. Although we are well aware of the myriad manifestations of this remarkable disease, it is nevertheless surprising that the intestine and pancreas almost invariably escape involvement. Haller and Walker in 1917, (Am. Jour. Med. Sc.) report ''Two Cases of Probable Syphilis of the Intestines.'' They exhibit a wise conservatism in inserting the word ''probable,'' and this excellent example is being followed in the title of this paper, namely, ''Chronic Diarrhea *Probably* Due to Syphilis.''

The patient whose history is to be related has been under observation from November, 1915, to March, 1919, or three and one-half years, and was studied at the University of California Medical Clinic and Hospital.

Miss H. F.: U. C. O. P. D. No. 19137. White, female, single, 26 years, waitress.

Her mother died of cancer of the stomach; otherwise there is no incident of significance in the family history. The patient was born in San Francisco and, except for 8 days, spent in Mexico, 13 years ago, has lived in California.

Measles and mumps as a child—otherwise no illness. No operations. Menstrual history—normal. Habits—2 cups of coffee and 2 cups of tea daily; occasional glass of beer or wine. Does not smoke.

Present Illness.—Diarrhea began one year before I saw her, and consisted of five to six watery stools daily. This condition lasted two months and then decreased in intensity to two to three loose movements daily which then persisted continuously until November, 1915, when she came to the medical clinic. She had observed constantly stringy mucous shreds, but never noticed blood in her stools. Her appetite was good. She had gradually lost 24 pounds, from 117 to 93 pounds. She frequently had abdominal pains of a colicky nature, but not consistently, and never localized to a particular region. She never suffered from nausea or vomiting, never experienced a sudden impulse to defecate, neither was defecation painful. She never had hemorrhoids and never noticed any discharge from her rectum.

Some physicians previously consulted had attempted treatment upon the bases of hyperthyroidism and achylia, but without improvement. Various diets were likewise unsuccessful.

The patient, despite careful questioning and readiness to impart information, gave no history of primary or secondary manifestations, though she admitted ''exposure.''

Physical Examination.—The patient was slender and undernourished, but fairly well developed. Careful general examination was entirely negative except for palpable kidneys. There were no signs of hyperthyroidism or Graves' disease, and no physical evidence whatever of syphilis.

Special Examinations.—*Stool*—Fatty stools, negative Benzidene, no ameba, no tubercle bacilli. The stools repeatedly examined always gave the above results.

Gastric Analysis—Free HCl-10, Combined—50.

Wassermann in blood serum—Positive +++ (very strongly positive).

Lumbar Puncture—Spinal Fluid—3 cells, Nonne and Noguchi and Wassermann—negative.

X-Ray Chest—Some infiltration throughout both lungs, considerable about roots —both apices clear.

Fluoroscopic Examination and Plates of Stomach and Intestines—negative.

Proctoscopic Examination—Revealed a few small internal hemorrhoids and a slight congestion of the mucous membrane high up in the sigmoid, but no ulcerations.

Clinical Course.—In order to give the therapeutic test a fair trial, no dietary restrictions were permitted. After 6 mercury salicylate injections and 0.4 old salvarsan, the number of movements decreased to one daily, but this one was still of loose consistency. She then received 22 mercury benzoate 2 per cent injections, and gradually gained 11 pounds from November, 1915, to November, 1916. By this time she had but one formed movement daily and felt much improved generally. She then disappeared for somewhat over a year and was not seen again until February, 1918. During this interval she had not had any treatment whatever and had not consulted any physician. She had not had any return of the diarrhea and had gained 11 pounds more—a total of 22 pounds since beginning treatment. She was again thoroughly examined at this time and found in excellent physical condition. She was then given 0.6 novarsenobenzol Billon, and had a slight reaction consisting of nausea and diarrhea for the two days following the injection. This occurred again two weeks later when 0.45 novarsenobenzol Billon was administered. Tiny veins made arsphenamine therapy extremely difficult.

She was seen again October, 1918, ill with pandemic influenza. There was no return of the diarrhea, and the influenza was of the respiratory type. By Nov. 15, 1918, she had regained the weight lost during the attack of influenza, and had added 3 pounds more—making a total gain of 25 pounds in three years.

Differential Diagnosis.—Malignancy can be excluded by the chronicity and subsequent gain in weight under treatment. There were no signs whatever of overactivity of the thyroid gland except diarrhea. The diarrhea was not due to achylia, and the administration of hydrochloric acid had been attempted without benefit. Amebic dysentery was probably not the etiologic factor, because ameba were never found despite repeated searching, and because proctoscopic examination did not reveal any ulceration. Tuberculosis of the intestines seems unlikely in the face of negative findings throughout the body—no evidence of tuberculosis in the lungs, no fever, no night sweats, no tubercle bacilli in the stools.

It would seem therefore that we are justified in assuming syphilis as the etioligic agent. The diarrhea disappeared under arsphenamine and mercury, without rest in bed or dietary restrictions—and the patient gained 25 pounds in weight. Whether the diarrhea was of intestinal or pancreatic origin is not clear, though the fatty nature of the stools suggests disturbance of the pancreas.

CONCLUSIONS

1. Chronic diarrhea of one year's duration was cured by arsphenamine and mercury.
2. Syphilis as the cause seems reasonable, since malignancy, tuberculosis, hyperthyroidism, achylia, and amebic dysentery can be excluded.
3. The patient gained 25 pounds and diarrhea has not recurred during three years of observation. No therapeutic measures of any kind were employed except arsphenamine and mercury.
4. The fatty stools suggest involvement of the pancreas.
5. A case is recorded of probable syphilis of the intestine or pancreas.

THE INCIDENCE OF SYPHILIS AS MANIFESTED BY ROUTINE WASSERMANN REACTIONS ON 2925 HOSPITAL AND DISPENSARY MEDICAL CASES

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THE following report is based upon 2925 Wassermann reactions done as routine on all medical cases admitted to Barnes Hospital and the medical clinics of Washington University Dispensary during the year 1918.

Of these, 675 were hospital patients. This does not include 456 patients admitted to the hospital during the recent influenza epidemic, upon whom routine tests were not done, due to the abnormal conditions existing at that time.

The dispensary cases numbered 2250. This includes patients from the general medical, gastrointestinal, and neurological clinics. It takes in only a few cases from the tuberculosis clinic, for Wassermanns from this clinic were done, together with tuberculosis complement-fixation tests, in another laboratory, using only a cholesterinized antigen and a different technic from that employed in our series.

The classification of results was undertaken at the suggestion of Doctor Dock, to determine the relative incidence of syphilis as manifested by the Wassermann reaction in four general classes of patients. We have considered, therefore, the following groups, as being representative of four social classes:

Group I. Private pavilion patients; the well-to-do class.
Group II. Pay ward patients; the middle class.
Group III. Free ward patients; the lower (white) class.
Group IV. Colored patients.

In the dispensary cases two groups were considered: white and colored. These again were divided into male and female of each race, and the cases coming from each clinic were grouped together to show the relative frequency of positive reactions from these services.

The technic employed in the tests performed was as follows:[1]

Three antigens were used; an alcoholic extract of syphilitic liver (1:10 dilution); a cholesterinized alcoholic beef heart extract (1:20 dilution); and the acetone insoluble lipoid antigen of Noguchi (1:20 dilution). The various antigen doses were in each instance determined by previous titration. A serum control was run on each test, 0.1 c.c. freshly inactivated patient's serum was added to each of the four tubes set up, 1 c.c. complement—fresh guinea pig serum, diluted 1:20—and 1 c.c. salt solution. The tubes were shaken and incubated one hour at 37.5°, dry heat. With the incubation an amboceptor titration was also made and 1½ times the unit of amboceptor thus determined was used as the dose in the final titration. One c.c. 2½ per cent suspension of sheep cells was used in both amboceptor titration and the hemolytic system. After adding amboceptor and sheep cells, the tubes were shaken a second time and again incubated for one hour. The results were read immediately.

The following controls were also set up:

1. A known positive serum.
2. A known negative serum.
3. A control on each antigen.
4. A control on the hemolytic system.
5. A control on the sheep corpuscles.

Reports were made on each antigen, using the symbols +, ++, +++, and negative.

All tests were done by one of us (McNitt).

In grouping the Wassermann results for this survey, we have separated into one group all reactions +4 in all antigens; into another those +4 in the cholesterin antigen with strong reactions in one or both of the syphilitic liver and Noguchi antigens, which we have called "strongly positive;" while a few incomplete reactions with the cholesterin antigen, also giving weak fixation with one or both of the other two antigens were classed as "weakly positive." The cases giving reaction with the cholesterin antigen alone were also grouped separately. A few reports were returned with negative blood, but positive spinal fluid reactions. There was also a small number of cases giving no blood reaction, but having unquestionable syphilis.

Table I shows the cases grouped under the headings described as regards the Wassermann reaction, and also separated into four classes: Private patients, pay ward patients, free ward patients, and colored.

TABLE I

INCIDENCE OF SYPHILIS IN 2925 HOSPITAL AND DISPENSARY CASES BY CLASSES

HOSPITAL—675 CASES									O. P. D.—2250 CASES			
Wassermann Result	P. P. 144 Cases		Pay Ward 380 Cases		Free Ward 91 Cases		Colored 60 Cases		White 1777 Cases		Colored 473 Cases	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
4 + All antigens	3	2	16	4.2	11	12	7	11.6	109	6.1	84	17.7
Strongly +	2	1.4	11	3	3	3.2	7	11.6	50	2.8	53	11.2
Weakly +									6	.3	3	.6
4 + Cholest.	2	1.4	12	3.2	2	2.1	3	5	78	4.3	46	9.7
3 + Cholest. 2 + Cholest. 1 + Cholest.	3	2	5	3.8	5	5.3	3	5	66	3.7	17	3.6
Pos. Sp. fl. Neg. blood	2	1.4	3	.8	0		0		4	0.2	0	
Total No. with Pos. Wassermann	12	8.3	47	12.6	21	23	20	33	313	17.6	203	42.7
Estimated Incidence of Syphilis	9	6.3	52	13.6	18	19.8	18	30	282	15.9	192	40.5
Neg. Wass. Pos. Lues	0		9	2.3			1	1.6	28	1.6	4	0.8
Neg. Wass. Lues Suspicious	3		15		4		7		104		44	
Negative	129		309		66		32		1332		222	
Totals	144		380		91		60		1777		473	

In figuring the percentage of positive reactions in each group, all giving a positive test were included. As will be discussed later in this report, the weak cholesterin positives are, when not substantiated by clinical evidence, doubtful proof of the existence of syphilis. In order to obtain a more exact estimate of the incidence of syphilis in each class of patients, therefore, only those cases having definite clinical evidence of syphilis were included among those giving Wassermann reaction 3+ cholesterin or less. Also cases having syphilis, but giving negative reactions are included. The figures thus obtained are shown under the heading "estimated incidence of syphilis" in Table I.

It will be seen that 6.3 per cent of the private patients, representing the upper social class, are estimated as having syphilis. Relating the results obtained in the other classes to this figure, the percentage for pay ward patients is about twice as high, for free ward patients, three times as high, and for colored patients, five times as high. Among the white dispensary patients, socially on about the same footing as the free ward patients, 15.9 per cent are estimated as having syphilis, a figure somewhat lower than the free ward incidence. The colored dispensary patients showed more than six times as much syphilis as private hospital patients.

To draw exact conclusions from such figures is impossible. But it is felt that they give an indication of the relative incidence of syphilis among the four social and racial groups considered.

The literature gives little information on the incidence of syphilis as shown by Wassermann reaction among the well-to-do class. McLester[2] found in a series of 300 consecutive private patients, 56 patients, or 18.8 per cent, giving positive reaction; 39 per cent of this number gave a more or less complete history of infection, 61 per cent gave no such history.

Numerous statistical studies have been made, however, on hospital and dispensary patients. Rosenberger[3, 4] found in 1916, 27 per cent positive reactions among 5,106 cases from the Philadelphia General Hospital; and in 1917, 25.9 per cent positive among 5,106 cases from the same hospital.

Using the cholesterinized antigen alone, Walker and Haller[5] found 12 per cent positive reactions among 1200 routine medical cases in the Peter Bent Brigham Hospital and Outpatient Department.

Vedder[6] in an examination of a large number of army men by routine Wassermann tests found among 1019 recruits 7.75 per cent undoubted syphilis and 16.77 per cent as the estimated total number of probable luetics, as shown by the Wassermann reaction.

McNeil[7] obtained 35 per cent positive reactions among 1200 negro males, all hospital cases. Purely medical cases (400) gave 40 per cent positive. In a series of 200 apparently healthy negroes 24 per cent were positive.

In order to ascertain what percentage of cases giving positive reactions gave also clinical evidence of syphilis, and in what percentage —no such evidence was found in the case records—Table II was constructed.

The Wassermann results were grouped as before. Under the heading, *"Clinically Negative"* were placed all cases giving no indication in the history or physical examination of syphilitic infection. A history of miscarriages, stillbirths, or childless marriage excluded from this group. So, also, any history of a penile sore, whether typical or manifestly atypical in description, excluded.

Clinically positive cases include all giving definite history of infection, with or without treatment, definite physical evidence of syphilis, or both.

Cases which could not be diagnosed clinically, but gave some hint as to the possibility of syphilitic infection were grouped together as "Clinically Suspicious." Many of these cases gave a history of a primary "sore;" a few gave history of treatment. A history of miscarriages, stillbirths or childless marriage put a case in this group.

TABLE II

TO SHOW THE RELATION BETWEEN THE WASSERMANN RESULT AND CLINICAL EVIDENCE OF SYPHILIS

WASSERMANN RESULT	NUMBER CASES	CLIN. NEG.	% CLIN. NEG.	CLIN. SUSP.	% CLIN. SUSP.	CLIN. POS.	% CLIN. POS.
4 + all antigens	230	39	16.9	51	22.5	140	61
Strongly +	126	19	15.1	30	23.7	77	61.2
Weakly +	8	1	12.5	3	37.5	4	50
4 + Cholest.	143	34	23.8	45	31.5	64	44.7
3 + Cholest.	21	7	33.3	11	52.3	3	14.3
2 + Cholest.	35	13	37.3	15	42.8	7	19.9
1 + Cholest.	42	17	40.5	22	52.2	3	7.3
Neg. Blood + Sp. Fl.	9	0		0		9	100
Total pos.	614	130	21.1	174	28.4	310	50.5
Neg. Blood	219	0	0	177	81	42	19

In drawing conclusions from this table, it must be remembered that histories, at best, are inaccurate regarding syphilitic infection, either because the patient withholds the truth, is ignorant of infection, or the examiner fails to ask specific questions. This is particularly true of dispensary histories. When no mention was made of specific history or physical findings, the case, if giving a positive Wassermann was classed as "clinically negative."

Considering the cases +4 in all antigens and those strongly positive, it is seen that about 15 per cent gave no clinical evidence of the disease. A still higher percentage of clinically negative cases is found among cholesterin positives, rising as the reaction becomes weaker. There may be several causes for this increase.

1. Errors in history taking. This, however, we may assume to be about equal in all groups, and probably has little influence.

2. A greater number of false positives among the weak reactions than among the strong. This is no doubt true and accounts in a large part for the difference in percentages noted. Only 7.3 per cent of the 1+ cholesterin cases were clinically positive, 44.7 per cent of the 4+ cholesterin cases, and 61 per cent of those giving strongly positive reactions. All of the clinically positive 1+ cholesterin cases were treated. A more careful analysis of the 22 clinically suspicious cases shows that 3 were negative on repetition, leaving 19 done only once. Of the 17 clinically negative cases, 3 were negative on repetition and 4 were negative after provocative treatment, leaving 10 in which the reaction was not repeated.

In the absence of good clinical evidence of syphilis, these repeated cases are undoubtedly not syphilitic and those not repeated were probably not syphilitics.

Of the 2+ cholesterin reactions 19.9 per cent were clinically positive; all had received treatment.

Fifteen were ''suspicious clinically,'' 5 of these were negative on repetition. One gave the same reaction on repetition. Two were positive on former tests, 5 were negative on repetition, and the remaining 7 had only one test done.

Of the 13 clinically negative cases, 5 gave negative reactions on repetition. The remaining 8 were not retested.

Summarizing the cases giving 1+ and 2+ cholesterin reactions, we can safely say that of 77 such cases, 10 had syphilis, 15 were not syphilitic as repeated tests were negative, and the remaining 52 probably did not have syphilis.

Of the cases 3+ with the cholesterin antigen, 3 had syphilis, 3 were negative on repetition and did not have syphilis, while 15 (6 clinically negative and 9 suspicious clinically) had only one test done.

Of the 4+ cholesterin cases, 64, or 44.7 per cent had syphilis clinically. Two of the 34 clinically negative cases were positive on repetition; one was negative after provocative treatment. All other cases were only tested once.

We can not draw any conclusions from these figures, when the record and not the patient is our only means of information. They emphasize the importance of careful history taking and of doing repeated tests on cases giving reactions with the cholesterin antigen only. In this way alone can we say whether or not such reactions, in the absence of clinical evidence of syphilis, are specific.

In a series of about 10,000 cases Ecker[8] reports 23.7 per cent positive Wassermann reactions among males and 24.99 per cent among females. Among colored patients 41.39 per cent of males and 42.85 per cent of females gave positive reactions.

TABLE III

WASSERMANN RESULT	NUMBER	WHITE MALES	WHITE FEMALES	COLORED MALES	COLORED FEMALES	MED. I	G. I.	NERVE	CHEST
4 + All antigens	193	66	43	42	42	114	35	40	4
Strongly +	103	25	25	29	24	65	15	22	1
Weakly +	9	4	2	2	1	5	1	2	1
4 + Cholest.	124	34	44	17	29	64	23	35	2
3 + Cholest. 2 + Cholest. 1 + Cholest.	83	38	28	5	12	47	12	22	2
Sp. Fl. only	4	2	2	0	0	1	1	2	0
Total Pos. Wassermann	516	169	144	95	108	296	87	123	10
Neg. Wass. Pos. Lues	32	20	6	4	2	14	2	16	0
Negative	1702	664	774	101	163	907	442	343	10
Totals	2250	853	924	200	273	1217	531	482	20
% Pos. Wass.	23%	20%	16%	48%	40%	24%	16%	26%	50%
Estimated Incidence of Syph.	21%	18%	14%	48%	36%				

Table III shows the percentage of positive Wassermann reactions in the sexes and races among 2250 out-patient cases. An estimate was also made of the probable incidence of syphilis by disregarding the cases giving positive cholesterin reactions less than 4+, except those clinically positive, and including cases having syphilis but giving negative Wassermann reaction.

Table III also shows the percentage of positive reactions and estimated incidence of syphilis in the cases from the general medical clinic (Med. I), gastrointestinal clinic (G. I.) and nerve clinic.*

C. N. S. SYPHILIS

One hundred thirty-four cases of neurosyphilis were encountered in our total series, or 20 per cent of all cases giving positive reactions (668) or definite evidence of syphilis without positive Wassermann (42). This figure agrees with the estimation made by Fordyce[9] that 20 per cent of all syphilitics would on careful examination be shown to have nervous system involvement. Parkin and Cornwall[10] feel that 30 to 40 per cent of those infected have syphilitic foci in the nervous system.

Of 13 cases giving reactions 3 + or less in the cholesterin antigen

TABLE IV

134 CASES OF C. N. S. SYPHILIS AMONG 2925 HOSPITAL AND DISPENSARY CASES

	C. N. S.		TABES		TABES-PARESIS		PARESIS		MENINGITIS (LUETIC)		
WASSERMANN RESULT	CLIN. POS.	CLIN. ?	CLIN. POS.	CLIN. ?	CLIN. POS.	CLIN. ?	CLIN. POS.	CLIN. ?	CLIN. POS.	CLIN. ?	TOTAL
Strongly +	38	2	18		2		8		2		70
4 + Cholest.	15	1	3		1		4	1			25
3 + Cholest.	2	3									5
2 + Cholest.	2	0					1				3
1 + Cholest.	2	2					1				5
Pos. Sp. Fl. Neg. Blood	2		1				1				4
Neg. Wass.	12	.	8		1		1 (treated)				22
Total	73	8	30	0	4	0	16	1	2	0	134
% of clin. pos. cases having pos. Wassermann	83.5%		73.3%		75%		93.7%		100%		

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*Note: Patients coming to the tuberculosis clinic had routine tests done, in conjunction with the complement-fixation test for tuberculosis, in a separate laboratory, using a different technic from that employed in our series. A cholesterinized beef heart antigen alone was used, of a less sensitive titer than ours.

I am indebted to Doctor J. J. Singer, physician-in-charge of the Tuberculosis Clinic of the Washington University Dispensary, for permission to use the following figures. The tests were performed under the direction of Doctor George Ives, by Miss D. Lamb:

CHEST CLINIC

Cholest. antigen	Number	Per cent
	102	11.3
	36	4.1
	35	3.9
	36	4.1
Negative	684	
Total	893	23.4% postive.

alone, 8 were clinically positive. It is well known that the cholesterin antigen is particularly valuable in cases of neurosyphilis.

Twenty-six cases gave negative blood Wassermanns, 4 of these gave a positive spinal fluid Wassermann; 6 had negative spinal fluid reactions. Of 22 negative blood reactions, including 6 with negative spinal fluid also, only three gave no history of treatment, 19, or 86.5 per cent, were treated cases.

SPINAL FLUIDS

Eighty-six spinal fluids were tested; 28 were strongly positive and 7 were positive in the cholesterin antigen only, though all cholesterin positives had clinical neurosyphilis. Thus 35, or 39.7 per cent, of the spinal fluids tested gave positive Wassermann reactions. Fifty fluids gave negative reactions. Of this number, 6, 7 per cent, had an increased cell count with positive globulin reaction, all in cases of clinical neurosyphilis. Thirteen, or 16.2 per cent, were normal on microscopic and chemical examination though all had clinical C. N. S. syphilis, only one being questionable. Of the 31 remaining cases, 4 had strongly positive blood reactions, in 5 there was a cholesterin reaction only; while in 22 the blood test was also negative. In these 22 cases, 3 were luetic, 8 nonluetic and 11 questionably luetic clinically.

DIABETES

There were 33 cases of diabetes; 7 gave positive Wassermann reactions; 3 of this number were strongly positive and admitted infection; one other was 4 + in all antigens but no history was obtained as the patient was in coma on admission. Of the other 3 cases, one was 4+ cholesterin and on repetition 1+. This patient gave definite physical evidence of syphilis. One case gave a 2+ cholesterin reaction; he admitted infection and treatment. The last case gave a 3 + cholesterin Wassermann, denied infection, but admitted gonorrhea. The spinal fluid was negative. The blood Wassermann was not repeated.

Therefore, out of 7 positive Wassermanns among 33 diabetics only one had an unexplainable weak cholesterin reaction.

MALARIA

Eleven cases of malaria gave 4 positive reactions, or 36.5 per cent. One case of tertian malaria was strongly positive and remained so after malarial treatment. Her Wassermann was still 3 + cholesterin six months after her malarial infection, which did not recur.

Two cases gave strongly positive reactions while in the acute stage of the tertian malarial infection. One was completely negative fifteen days later without any treatment except quinine. The other became 1 + cholesterin one month later with the same treatment. Neither case gave any clinical evidence of syphilis. It seems probable, therefore, that these two cases gave strongly positive reactions due to malarial infection and not to syphilis. A more detailed report of these cases follows:

A. M., Med. No. 4336, white, female, age 36, married.

Patient entered Barnes Hospital, July 19, 1918, at noon, complaining of "chills and fever." She gave no history indicating luetic infection, had been pregnant four times, with three children living and well; one died in infancy. No history of miscarriages. The general physical examination was negative. Blood smears examined on day of admission showed tertian malarial parasites. Later blood examination and temperature showed presence of a double tertian infection. Blood was taken for the serologic tests on the 19th about 6 P.M. when the temperature was 103.8° (rectal).

Quinine was begun on July 21, and the patient was discharged, apparently well on July 26.

Wassermann reaction:

Luetic alcoholic antigen	+
Cholesterin antigen	++++
Noguchi antigen	++++

Complement-fixation test for tuberculosis, positive +++. Wassermann reported from the tuberculosis laboratory was also ++++ (cholesterinized antigen).

The patient returned to the tuberculosis clinic of the dispensary on August 8, and blood was again taken for serologic examination. The report showed the luetic and Noguchi antigens negative, with positive 1 + in the cholesterin. No antiluetic treatment had been given.

C. H., Med. No. 4307, colored, female, age 24, single.

Patient entered the hospital, July 8, 1918 from the Out-patient Department, where malarial parasites were found in blood smears. Complained of "chills and fever" and gave a history of similar attacks in 1911 and 1917. Family history negative. Physical examination was negative. Blood smears taken on day of admission showed tertian malarial parasites. Blood was taken for Wassermann and tuberculosis complement-fixation tests on July 9, during a typical malarial temperature rise. Quinine begun this same day, controlled the fever and symptoms and the patient was discharged apparently well, on July 14.

Wassermann reaction:

Luetic alcoholic antigen,	positive	+
Cholesterin antigen	"	++++
Noguchi	"	++++

Complement-fixation test for tuberculosis, positive ++. Wassermann reported from tuberculosis laboratory, also ++++ (Cholesterinized antigen).

On July 23, 1918, patient reported at the skin clinic for antiluetic treatment. Blood was taken for Wassermann on that day, two weeks after the first test, and the reaction was negative in all antigens.

The complement-fixation test for tuberculosis was not repeated. There were no symptoms of malarial infection noted at the time of the second Wassermann.

CONCLUSIONS

Two thousand nine hundred twenty-five hospital and dispensary patients were subjected to a routine Wassermann test during the year 1918. From a detailed examination of the results obtained the following conclusions seem justifiable:

1. The incidence of syphilis as shown by the Wassermann reaction was lowest among the well-to-do, about twice as high among the middle class of society, represented by the pay-ward patients, and about three times as high among the lower social class, or free-ward patients. The incidence of syphilis among colored patients was about six times that among private patients.
2. About 15 per cent of cases giving strongly positive reactions gave no clinical evidence of syphilis. This percentage increases with the cholesterin positive cases, indicating that a certain number of cases giving weakly positive Wassermann reactions with the cholesterin antigen only did not have syphilis.
3. The percentage of clinically positive syphilis is highest in the strongly positive group (61 per cent) and lowest in the +1 positive cholesterin cases (7.3 per cent).
4. Weak reactions with the cholesterinized antigen are of value only when there is a definite clinical evidence of syphilis, in treated cases, or in cases of neurosyphilis.
5. Of 853 white males, 30 per cent gave positive Wassermann reactions; of 924 white females, 16 per cent were positive. Among colored patients 48 per cent of 200 males and 40 per cent of 273 females gave positive Wassermann reactions.
6. Among 7 cases of diabetes giving positive Wassermann reactions, only one did not give clinical evidence of syphilis.
7. Of four cases of malaria giving positive Wassermann reactions it seems probable that two of the positive reactions were due to malarial infection and not to syphilis.

In conclusion, we wish to express our thanks and appreciation for the many helpful suggestions given by Doctor Dock throughout the preparation of this paper.

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DELAYING THE EARLY DIAGNOSIS OF SYPHILIS (CHANCRE): THE DANGERS AND HOW TO AVOID THEM

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IT is unfortunate that the primary lesion of syphilis should make its earliest appearance as an innocent looking pimple or scratch, and usually without pain. This fact, with the ten days or longer primary incubation period, induces a *laissez faire* attitude on the part of the patient until either the lesion assumes larger proportions, or until the systemic manifestations make their appearance. In my experience the same state of mind exists on the part of some physicians, in regard to a patient with a suspicious looking sore; with this difference, that instead of waiting for the appearance of the macular eruption, sore throat, etc., they await the positive result of the Wassermann test, before treatment is instituted. It is the purpose of this paper to emphasize the dangers of this procedure and the methods to be used in avoiding them.

The ability to recognize the clinical appearances of the various types of the fully developed chancres, must always be cultivated to the highest degree to maintain a diagnostic acumen, but as such fully developed lesions commonly show a positive Wassermann in the blood of their possessors, so a needless loss of time is incurred in waiting for the classical clinical picture to appear in an otherwise suspicious looking sore. True, most of these delayed cases are cured, according to the modern methods of determining that fact, but occasionally a setback occurs, i.e., a return of a positive Wassermann after being negative, with or without the appearance of clinical symptoms, thus necessitating further treatment. Such relapses also occurred with the older mercury therapy and Hutchinson[1] recommended the use of mercury at the earliest possible moment in order to avoid these relapses, then the only criterion as to the efficacy of treatment.

The purpose of antiluetic treatment today is to prevent relapses, early or late, clinical or laboratory, in other words to cure the patients.

It is, however, necessary for us in order to give the patient every possibility for his cure, to establish the diagnosis at the earliest moment, and that is before the reagin or Wassermann bodies appear in his blood. The element of time is therefore of great importance, for the lymphatic system is early invaded,[2] and even the cerebrospinal fluid shows changes in some cases before the secondary rash appears.[3] Of course the patients must be taught to report for immediate examination and observation, but on the physician who treats syphilis rests the greater responsibility. He should learn to use the methods for detecting the Spirochete pallida (Treponema pallidum) in suspicious lesions, or avail himself of a reliable worker in that field at the earliest possible moment, when the occasion arises.

There are still a few who doubt that the spirochete pallida is the cause of syphilis, because the four laws of Koch are not completely fulfilled. They do admit the association of the organisms in luetic lesions. It is safe to say that organisms demonstrated as present in every type of luetic lesion, congenital and acquired, are not only in bad company, but actually one of them. A great mass of clinical and experimental evidence exists to warrant the assertion that no matter where the Spirochete pallida are in the human system, viscera or pimple, that patient is luetic who harbors them. The four laws of Koch are not fulfilled in the case of the Bacillus lepra, yet no one doubts the cause of leprosy. From a practical standpoint, in typical chancres that have not been tampered with, the Spirochete pallida will invariably be found if the search is continued long enough. Klauder[4] found them in 93.9 per cent of chancres not more than ten days old. In the past eight years I have made many a dark-field examination in suspicious and definite clinical chancres, mucous patches, etc., and I can only confirm the reliability of a positive finding.

In suspicious lesions of comparatively long duration, which are practically healed and to which spirocheticidal remedies are being applied, the organisms may be absent, here one must of necessity wait for the result of the Wassermann test, provided no clinical manifestations are visible.

Having such accurate means at our disposal to determine the early presence of syphilis, it is imperative to examine the secretion from every genital sore and suspicious extragenital lesion with the dark-field, and continue the examinations until a positive finding occurs or until the lesion is healed. The patient then must be carefully observed for any clinical signs and Wassermann tests carried out every week for about two months more, when if all tests are negative and no systemic signs are present, the patient may be regarded as not a case of lues.

Considerable delay can be avoided if physicians will discontinue the practice of applying strong remedies to lesions which they wish examined for spirochetes. It can not be too strongly emphasized that in order to establish a clinical as well as a laboratory diagnosis of a chancre, all applications except a normal saline or plain water dressing, should be withheld; for applying nitric acid, calomel, etc., only adds an artificial induration and renders it very difficult to find the spirochete. A delay in the examination for the organism owing to a previous strong application to the sore, may mean the difference between a negative and positive Wassermann in the patient's blood.

With a positive dark-field it is not necessary to wait for a positive Wassermann before treatment is started. If you do, you not only confirm what is already known, but also establish a generalized distribution of the organism throughout the tissues, with possible dire results.

The laboratory examination is also of great aid in mixed sores, urethral lesions, tonsillar affections, as well as extragenital lesions resembling boils and deep ringworm. It has happened more than once, for an observer to be shocked by the appearance of a syphilitic roseola, because the primary sore was of an atypical appearance. Nowadays many patients realize how serious a disease syphilis is, and they feel bad enough when told that they have a chancre, how much worse must they feel when told that the outbreak present on their body or in their mouths is the result of a sore on their genitals or elsewhere, which they were led to believe was of no importance.

Of the many methods in use to detect the Spirochete pallida, the dark-field is the most simple, rapid and accurate. This method is excellently described by Harrison[5] and also by Wright,[6] and with practice is no more difficult than a Gram's stain for the gonococcus. It should be in the equipment of every physician who treats venereal diseases, and if this were a fact, the diagnosis would probably be established very much earlier than it is at present. The examiner should acquaint himself with the appearances of other types of spiral organisms, especially the buccalis calligyrum, refringens, Vincent's, etc., so as not to fall into error and cause the patient unnecessary anguish.

In the history of the treatment of syphilis, whatever plan was followed, it was always recognized that the treatment was to be started as soon as the diagnosis was established. The modern methods of diagnosis and therapy at our disposal place in our hands agents for the complete eradication of the disease in time, as we are able to make the diagnosis of lues at its very inception, and we have the means to annihilate the causative organism. But—we must get at the spirochete before he scatters his forces, in order to be assured against his further onslaughts.

Fordyce, Pollitzer, and others with large experience, both in this country and abroad, consider the chances for a permanent cure as best in those cases with a primary lesion and a negative Wassermann. The plan of treatment in such early cases is not the subject of this paper, but I may be allowed to say that it should consist of the energetic administration of arsphenamine and mercury, with due regard to the patient's constitution. If, with a chancre and a negative Wassermann, one finds the reaction turning positive after an injection of arsphenamine, it is fair to assume that the case was a little older than was suspected, but the chances for a permanent cure are still at their best.

Let us now pass to the cases with a lesion, genital or extragenital, where either through neglect of the patient. or through doubt or delay on the part of the physician, the Wassermann is allowed to become four-plus, with or without the appearance of systemic manifestation. Following the same plan of treatment used in the early cases, the majority of this class of patients remain free and we hope permanently so, of all clinical symptoms with negative Wassermanns in serum and spinal fluid. But there is this difference between the early case with a negative Wassermann and the later case and a positive Wassermann, and that is the possibility in the latter of a relapse; this although admittedly rare, is nevertheless to be considered. It is of importance then to get your patient under treatment, where his or her chances are of the best.

The following history will illustrate what a difference in results is possible between the chancre-Wassermann negative case and the chancre-Wassermann positive case:

Mrs. B. B., presented herself June 24, 1913, with a chancre of the left labia um major and inguinal adenopathy, all of five days' duration. The dark-field was positive and her Wassermann was negative. Examination of her husband showed a small scaly papule of about six weeks' duration on the right side of his glans penis, a positive Wassermann, and no systemic signs. His wife after two injections of arsphenamine, and ten of mercury salicylate, was free of all symptoms, with numerous Wassermann tests all negative. She refused any further treatment. On the contrary her husband in spite of active and continuous treatment, developed cerebrospinal lues, although of a mild type.

The following history is cited to show a relapse in a chancre-Wassermann positive-macular case, while under active treatment:

Mr. A. F., presented himself Nov. 16, 1918, with an initial lesion on his penis, macular rash on his body and a four-plus Wassermann. He received seven injections of arsphenamine, 0.4 each, and ten injections of mercury salicylate, all in six weeks. After that his blood was negative and he was asymptomatic. About six weeks later he received another course of six injections of arsphenamine and ten injections of mercury, and so far he has been asymptomatic with a negative Wassermann. When he first came to me, his wife was about to be confined, and I pleaded with him to bring her to me for examination, but he did not until the baby was about eight weeks old, when both the mother and the baby were covered with a macular rash. The mother's Wassermann test was positive. The baby did well under mercury rubs and two intravenous injections of arsphenamine, but the mother developed a sclerosing keratitis of the left eye during the end of her first course of treatment and in spite of it.

Those who are inclined to doubt the value of the arsenical treatment as carried out in recent years may choose to cite these cases as an example of its failure. I am not one of those, for all syphilologists know them to be rare occurrences; exceptions that prove the rule. That they are a possibility and must be taken into consideration is the only reason for citing them, in order that they may be avoided by making an early diagnosis.

To relate that relapses occurred with the older mercury treatment, no matter how early they were started on treatment, would be superfluous. Such relapses were absent in the early stages of the disease but made their appearance later on. The following history is of interest in this connection:

Mr. A. A., contracted a chancre nine years ago. His treatment was delayed until his Wassermann became weakly positive. He used mercury rubs for almost three years, but received no arsphenamine injections. He considered himself cured, and consulted no one until April 19, 1919, when his Wassermann was four-plus and clinical examination showed him an early paretic.

CONCLUSIONS

It is wiser to examine every suspicious lesion as early as possible for the Spirochete pallida (Treponema pallidum), using the dark-field as the most convenient and accurate method, refraining from the application of strong remedies until the diagnosis is established.

It is not necessary to wait for the appearance of a positive Wassermann before treatment is instituted, as a positive dark-field is sufficient evidence of the presence of lues.

With repeated negative dark-fields, Wassermann tests should be done every week for two more months, with careful clinical observation, before the patient is considered nonluetic.

The danger in delaying the diagnosis is the dissemination of the Spirochete pallida throughout the tissues, necessitating prolonged treatment in some cases, with the possibility of relapses in vital structures.

The chancre-Wassermann negative cases are considered preeminently favorable for a permanent cure.

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SYPHILIS AMONG THE INSANE WITH SPECIAL REFERENCE TO THE HECHT-WEINBERG-GRADWOHL TEST

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WHEN Gradwohl first introduced his modification of the Hecht-Weinberg test, I tried it out on something over 100 cases. These cases were transient patients of whom I could get no history and many of them were not aware that their blood was to be examined for syphilis. Among these cases I found a variation in the Wassermann and Hecht-Weinberg-Gradwohl tests. The Wassermann proved to be negative in some cases with typical chancres and the Hecht-Weinberg-Gradwohl positive; a condition which would tend to prove the presence of thermolabile antibodies which are the first to appear in the blood, and as will be shown later in the article that they are the last to disappear.

The cases examined in this hospital had their blood taken in every case a day before the test was to be made, and the tubes kept in the ice chest overnight, thereby insuring a fresh serum. Previous to performing the Hecht-Weinberg-Gradwohl test, I tried out the Wassermann on over 200 fresh serums to determine the effect of inactivating the serum. These serums were titrated for complement and amboceptor content before the test was done, as follows:

For Complement

Tube No.	1	2	3	4	5	6	7	8	9	10	
Fresh Serum	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	c.c.
Complement (1-20 dilution)	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	c.c.

Amboceptor 2 units in each tube.
Cells
(5% Emulsion) 0.5 c.c. in each tube.

For Amboceptor

Tube No.	1	2	3	4	5	6	7	8	9	10
Fresh Serum	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1 c.c.
Complement	1 unit in each tube.									
Amboceptor (1-1000 dilution)	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0 c.c.
Cells (5% Emulsion)	0.5 c.c. in each tube.									

By these titrations I determine the exact quantity of complement needed and the amount of amboceptor, and the tube in the first table showing the complete hemolysis is the amount of complement used, and the tube in the second table showing the complete hemolysis is the amount of amboceptor used. By using the unheated serum, I have found three plus and four plus reactions with the Wassermann test when the same cases with the same tests were negative and some two plus when the serums were heated. It is evidently seen that some syphilitic amboceptor must be present to unite with the antibodies and bind the complement which amboceptor was destroyed by heating. These variable cases also show a four-plus Hecht-Weinberg-Gradwohl test.

Noguchi[1] showed that the syphilitic antibody is much reduced by heating to 45° C.; also that 50° C. would reduce it to one-half, and 55° C. to one-fourth. He showed that at 56° C. the antibody is reduced to about one-third of the original in five minutes—over thirty minutes it is reduced to about one-fourth and at the end of one hour is reduced to about one-tenth of the original.

In the cases tabulated, all of the serums used were fresh, never over twenty-four hours old. The blood is collected from every case admitted on certain days at the same time in the afternoon, and kept in the ice chest overnight and the test done the next morning.

My technic is similar to that given by Gradwohl,[2] which is as follows: Place in a test tube stand twelve small test tubes. The first eight tubes are used for the determination of the hemolytic index of the serum. The last four tubes are used in the test. Add 0.1 c.c. of fresh unheated serum to each tube. Then add increasing amounts of 5 per cent suspension of sheep's cells. Start with 0.1 c.c. and end with 0.8 c.c. Then add enough saline to each tube to make a whole volume 1.0 c.c. To the last four tubes add as follows: 9th, 10th, and 11th tubes 0.1, 0.2, and 0.3 c.c. of diluted Noguchi's acetone-insoluble antigen, respectively. To the 12th tube is added only the serum and salt solution. After one hour's incubation at 37° C. in the water-bath the hemolytic index is read on each serum and ONE-HALF the indicated dose of cells added to the remaining four tubes of each series. After incubation for another hour the results are read and recorded. I only use eight tubes for titration of the hemolytic index instead of ten, as I have very seldom seen a serum which will cause hemolysis of over 0.7 c.c. of blood, as the average is usually 0.3 c.c. and 0.4 c.c.

It has been stated that the presence of antisheep amboceptor in the blood of persons depends, it is assumed, on the ingestion of mutton, and that it is impossible to state just how much mutton must be ingested before it appears. As we can control the ingestion of mutton among the patients here, the ingestion of mutton was found to have no effect upon the antisheep amboceptor as the ones who had none for some time had as much and some of them more antisheep amboceptor than the ones who consumed it. Furthermore, this cause was completely eliminated to my satisfaction when I used guinea pig cells, rabbit cells, mice cells and rat cells, and many of the sera contained natural hemolysins for each of the cells and in many cases enough to perform the Hecht-Weinberg-Gradwohl test. The objection to most of these cells in my work was that they were not as stable as the sheep's cells; as prolonged incubation would cause hemolysis in the control tubes.

I have used the Hecht-Weinberg-Gradwohl test parallel with the Wassermann test in over 1300 cases and have tabulated 1213 cases—as the cases showing insufficient native complement and amboceptor for the test and anticomplementary serums were thrown out of the tables. Gradwohl[3] has found that the sera of 98 per cent of persons contain some antisheep hemolysis. In his test if 0.1 c.c. of serum fails to hemolyze, 3.0 c.c. of a 5 per cent suspension of sheep's cells the results are regarded as of doubtful value. I have not been as successful in finding that high percentage of antisheep hemolysis in the blood serum, and it can not be attributed to old serum. Among 1299 sera I have found 1213 sera with sufficient antisheep hemolysis to hemolyze at least 0.2 c.c. of 5 per cent emulsion of sheep's cells and 86 cases with not sufficient antisheep hemolysis to even hemolyze 0.1 c.c. of cells, making 93.3 per cent of cases with enough antisheep hemolysis to give an accurate test. Out of the 86 cases which failed to completely hemolyze 0.1 c.c. of cells there were 73 of the sera which caused absolutely no hemolysis of the cells. Practically all of the sera which contained no hemolysis were turbid serums, and why the turbid serums seem to have no antisheep hemolysin, I can not explain.

The Wassermann test used in connection with the Hecht-Weinberg-Gradwohl test is the slight modification of the original Wassermann. For illustration, I shall give in brief the test used: Antigen—Noguchi's acetone insoluble—alcoholic extract of beef hearts—cholesterinized alcoholic extract of beef hearts (0.2 per cent cholesterin). The mixed complement from 3 to 5 guinea pigs, the amount used according to titration as the complement is always titrated previous to each test. Antisheep amboceptor 2 units. Patient's serum 0.1 c.c. inactivated at 56° C. for one-half hour. Controls from strong positive cases and the mixed serum of several known negatives. Five-tenths c.c. of 5 per cent sheep's cells collected sterile in (ten times its volume) 0.85 per cent salt solution containing 2 per cent sodium citrate, and washed in large dilutions. I formerly washed cells two, three, and five times, but have found that washing them only twice after throwing down the citrate solution, and using the 100 c.c. centrifuge tubes to keep high dilution of the cells gives better results than repeated washings. The repeated washings tend to weaken the cells, thereby causing them to be more readily hemolyzed. I have shown this to be the case in a series of experiments by washing cells from four to six times and putting them in the ice chest with unwashed cells collected at the same time and under the same conditions, and they will show presence of hemolysis within one to three days, while I have kept cells in sterile 2 per cent citrate saline solution from five to ten days on ice without any signs of hemolysis. But I have noticed this to vary with different sheep. Some sheep cells will keep from ten to fourteen days and others only two or three days, the average being six days if collected and kept sterile. On account of the varying resistance of the cells from different sheep, I use the same sheep, about two-thirds grown for several months and then change and in making antisheep amboceptor I use the blood of five to seven different sheep, according to the number of injections, and with the amboceptor get more uniform work.

In regard to the effect of treatment upon the Wassermann reaction and the Hecht-Weinberg-Gradwohl reaction in acquired syphilis the following case will illustrate: A woman whose husband was admitted to this hospital for paresis came to me for a blood examination to see whether she had acquired syphilis from her husband. The results of the test were a negative Wassermann and four-plus Hecht-Weinberg-Gradwohl test. After making the test, I learned that her blood was reported negative by her family physician, but he had only the Wassermann test done on her blood and after giving her antisyphilitic treatment. Later I learned that her family physician suspecting she would have her blood tested in this laboratory gave her a dose of salvarsan. Three weeks after the administration, I took the blood and found the above results. Therefore, the modified Hecht-Weinberg-Gradwohl test proved the case to be a positive one in spite of the fact of the treatment to feign a negative result.

Among the cases tabulated I found 16.5 per cent positive Hecht-Weinberg-Gradwohl and 12.47 per cent positive Wassermann tests, excluding those of paresis. It is evident that a person suffering from any psychosis may also be syphilitic, and that a positive blood Wassermann does not necessarily mean a psychosis of syphilitic origin, but it is our custom in cases with positive serums to examine the spinal fluid.

In paresis and taboparesis a strong reaction is almost constant in both blood and cerebrospinal fluid. Among the cases examined I found 98.5 per cent of paretics with positive Hecht-Weinberg-Gradwohl tests and 97.01 per cent with positive Wassermann tests. In order to illustrate the variation between the Hecht-Weinberg-Gradwohl and Wassermann reaction on the blood and spinal fluid, I will give the following cases of paresis:

CASE NUMBERS	WASSERMANN BLOOD	HECHT-GRADWOHL BLOOD	WASSERMANN SPINAL FLUID
9057	+	++++	++++
9355	++	++++	++++
9753	++	++++	++++
9629	++	++++	++++
9342	+++	++++	++++
9647	++	++++	++++
9669	+++	++++	++++
9030	++++	++++	++++
8394	+++	++++	++++
7921	++	++++	++++
7051	+++	++++	++++

Kirchberg[4] has examined the blood in 100 cases of paresis and found a positive reaction in 93 per cent of the cases. F. S. Hammond[5] found 87.14 per cent of positive in 70 serums of paresis and 87 per cent of 57 spinal fluids. Marie, Levaditi and Yamanouchi[6] found only 59 per cent positive serum reactions in 30 paretics, while in the spinal fluids 93 per cent were positive. Plaut and also Boas[7] each obtained 100 per cent positive blood serum reactions in 180 and 42 cases, respectively, although later Plaut admitted in his more extended series that he did not always get a positive result.

In this country, Kaplan's and Kaliski's[8] findings in each of their series showed respectively 65 per cent and 66 per cent positive blood reactions, while Rosenoff and Wiseman[9] obtained only 49.3 per cent positive results in the serum with 76 per cent positive in the fluids. Nonne's[10] results were 90 per cent positive in both blood and fluid.

From the tables tabulated by Noguchi[11] representing the work of 26 individual observers working independently, the average result of 660 serum examinations and 481 spinal examinations in general paralysis show 84.5 per cent positive reactions in the blood and 91 per cent positive reactions in the spinal fluid.

The presence of a negative Wassermann would make a diagnosis of paresis highly improbable; although I have found two cases of undoubted paresis with negative Wassermann tests and one with negative Hecht-Weinberg-Gradwohl test. Darling and Newcomb[12] quote eight cases diagnosed as paresis and the blood Wassermanns were negative and most of these cases were verified by autopsies. Plaut[13] in his book on the *Wassermann Reaction in Psychiatry* states that a negative Wassermann reaction where general paralysis is thought of, may be considered as significant as the absence of this disease. Carl With[14] found one negative among eleven paretics who had received no antisyphilitic treatment, but where the diagnosis is almost certain and the several times repeated findings of a negative reaction in the serum. This case probably forms an exception to Boas's rule.

In regard to the effect of antisyphilitic treatment on the Wassermann reaction in paresis it has been my experience to find that it has little effect upon the Wassermann as well as the Hecht-Weinberg-Gradwohl reactions. Plaut[15] was unable to detect any diminution in the reaction in the serums or cerebrospinal fluid—although a great fall in the cell content will occur. Carl With[16] obtained two faintly positives in 11 sera after intensive treatment. In a series of cases Evans and Thorne[17] were unable to obtain in paresis a negative Wassermann reaction either in the blood or cerebrospinal fluid. Some of their cases give a weakly positive or a faintly positive, but they always return to positive.

In 1913 Plaut, Rehm, and Schottmuller[18] stated that previous to the introduction of salvarsan no effect was obtained in paresis by antisyphilitic treatment. With salvarsan, however, a distinct diminution in the reaction of the cerebrospinal fluid may occur and in rare cases may become negative. Boas obtained a negative reaction in the serum of one case among a series of 243 cases, after intensive treatment with mercury and salvarsan.

Fildes and McIntosh[19] have pointed out that variations in the reactions without treatment may occur on account of "natural protective processes" without any active medical intravention. In a few cases the same is true among the cases in this hospital as it is usually the custom to examine the positive Wassermanns at intervals from six months to one year, and some cases have shown variations which have received no treatment, changing from four-plus to three-plus, and one-plus, and also from one-plus on up to four-plus. These cases seem to have no relation to the condition of the patients, that is, the serum may show a four-plus Wassermann reaction when the patient is clinically better than at the time the blood Wassermann reaction shows a two-plus or three-plus, but the cerebrospinal fluid has always remained four-plus among the cases.

Edwin Goodall[20] says "from these observations it appears that there is no correlation between the reaction and a state of reactions," a positive reaction being obtained in this state as often as a negative.

Leradle[21] has devoted particular attention to the effects of antisyphilitic treatment in the cases of paresis. He reported thirteen cases, in several of which both the symptoms and Wassermann reaction and serum were favorably influenced. Purves and Stewart[22] treated seven cases of paresis with injections of salvarsan both intracranially and intravenously and write that "before coming to any definite conclusions as to its effect we required numerous and prolonged observations over a large series of cases."

Although systematic work along that line has not yet been carried on here, the records show no grounds for regarding treatment as reducing the Wassermann reaction, as the few that show a difference in the Wassermann reaction after treatment can be balanced with similar variations among those who have received no treatment. In general, it may be said that antisyphilitic treatment does not exercise any definite effect upon the Wassermann reaction in paresis, while in taboparesis a diminution may be more frequently met with. For the purpose of illustrating the result of antisyphilitic treatment the following case came to this hospital with a three-plus Wassermann, four-plus Gradwohl and four-plus spinal fluid and all clinical symptoms of syphilis, after an intensive antisyhilitic treatment.

Case No. 8689.—J. P. C.

Family History.—Father was born in Cuba. Died at age of eighty-two years of heart attack. Mother died at age of sixty-eight of anemia. Brothers all living and in good health. Sisters all living and in good health. No history of insanity elicited in family.

Personal History.—Early life was healthy. He attended high school and received a good education. An accountant by profession. Single. Contracted syphilis at age of twenty-two years.

Psychosis.—Began in September, 1916. At this time he was morose and quiet. Did not take the same interest in affairs that he formerly had. When talking with others he would fall asleep. In driving his car he would have minor accidents which he never had before. He was taken to a sanitarium in 1916 and given various injections of salvarsan. He remained there about four months. He came home and remained home about three months, and did not pay attention to his work. Was grandiose and quite exalted. He was taken to New York where he received intensive antisyphilitic treatment and was given intracranial injections. He had ideas of great wealth and showed fear. Thought he was to be killed and that people were after him to operate on him.

Mental Status.—Patient lies in a listless manner. Does not recognize his surroundings. Displays no interest or activity. Is dull and refuses to obey simple commands. Movements very slow and involuntary. His attention can not be aroused. He is quiet and does not answer any questions, but at frequent intervals mumbles indistinctly.

Gradwohl[23] quotes a number of cases where treatment gave a negative Wassermann without any effect on the Gradwohl test. Two of his cases were taboparesis, but one of the cases quoted was paresis. In cases similar to ones Gradwohl quoted I have found that treatment would bring the Wassermann test negative, one-plus, two-plus, three-plus, with the Gradwohl reaction four-plus as shown in some of the cases of the table with negative, one-, two-, three-plus Wassermann reactions and four-plus Gradwohl reactions.

Fildes and Fearnsides[24] remark that in paresis it is possible that the degeneration of the nerve tissues continues the type of the initial reaction, thus is "specific" giving rise continually to the Wassermann body.

TABLE I

THE RESULTS OF THE TESTS ON THE BLOOD SERUM

PSYCHOSES	NUMBER OF CASES	HECHT-WEIN.-GRAD.			WASSERMANN REACTION			
		Pos.	Neg.	% Pos.	Pos.	Dbtfl.	Neg.	% Pos.
Dementia precox	442	67	375	15.15	55	7	380	10.18
Manic depressive	116	17	99	14.65	13	4	99	11.20
Senile psychosis	92	14	78	10.52	11	3	78	10.19
Imbecility	83	11	72	13.25	9	1	73	10.84
Epileptic psychosis	130	14	116	10.76	11	0	119	8.46
Melancholia involutional	56	6	50	10.71	4	2	50	7.14
Paresis	67	66	1	98.50	65	1	1	97.01
Alcoholic psychosis	48	8	40	16.66	5	1	42	10.41
Psychosis with brain lesion	57	12	45	21.05	8	4	45	15.26
Melancholia	7	0	7	00.00	0	1	6	00.00
Imbecility with psychosis	10	3	7	30.00	3	0	7	30.00
Depression—undifferentiated	11	4	7	36.36	3	1	7	27.27
Paranoia	12	1	11	8.33	1	0	11	8.33
Psychosis with cerebral sclerosis	6	2	4	33.33	2	0	4	33.33
Infective exhaustive psychosis	12	2	10	16.66	2	0	10	16.66
Alcoholic hallucinatory	14	5	9	35.71	3	1	10	21.42
Drug habitue	2	0	2	00.00	0	0	2	00.00
Gross brain lesion—post apoplectic	5	1	4	20.00	1	0	4	20.00
Dementia	7	1	6	14.28	1	0	6	14.28
Constitutional inferiority	8	1	7	12.50	0	0	8	00.00
Toxic psychosis	7	2	5	28.57	2	0	5	28.57
Epileptic imbecile	4	0	4	00.00	0	0	4	00.00
Cerebral syphilis	12	12	0	100.00	9	3	0	75.00
Presenile delusional insanity	2	0	2	00.00	0	0	2	00.00
Gross brain lesion—arteriosclerosis	3	1	2	33.33	0	0	3	00.00
TOTAL	1213	250	963	20.61	208	29	976	17.14

On the other hand, a more probable explanation is to be found in the fact that antisyphilitic remedies do not readily obtain access to the spirochetes lying in the nerve tissues.

W. H. Wilcox has already demonstrated that after treatment with salvarsan though all of the viscera contain large quantities of arsenic it was entirely absent from the brain. McIntosh and Fildes[25] also used injection of arsenic and analine dyes with similar results.

Therefore, it is evident that the Wassermann reaction will remain unaffected in spite of the antisyphilitic treatment if the focus of the Wassermann substance lies within the original tissues of the brain. The cellular infiltration of the meninges, dependent upon the activity of this focus will remain unaffected by treatment and will determine the injury to the pial covering which lines the passage of the Wassermann substance into the cerebrospinal fluid.

ANALYZATION OF RESULTS

The results of the tests on the blood serums are summarized in the accompanying tables.

In commenting upon Table I, one will note that there are none quoted as doubtful test in the Hecht-Weinberg-Gradwohl reactions: as the cases showing one-plus or a doubtful reaction with the Wassermann test, the Hecht-Weinberg-Gradwohl usually determines whether it is negative or positive. For example a test with one-plus reaction and negative Hecht-Weinberg-Gradwohl reaction, is reported as a negative test, and test with a one-plus Wassermann and four-plus Hecht-Weinberg-Gradwohl is repeated and reported according to the second finding.

It is, of course, true that a single negative reaction does not exclude syphilis, neither does a single positive reaction constitute any doubtful evidence for infection, but cases with negative reactions with a suspicion of syphilis are done over and cases with positive reactions with no suspicion of syphilis are also repeated. Repeating the test with both Wassermann and Hecht-Weinberg-Gradwohl reaction gives more accurate data.

Gradwohl[26] found approximately 15 to 20 more positives with this method than with the Wassermann test. He states that in no case out of 10,000 cases has the Wassermann test ever been positive and the Hecht-Weinberg-Gradwohl, negative. Among the cases I examined, I have found six cases with a four-plus Wassermann test

TABLE II

PSYCHOSIS BY SEX

PSYCHOSES	MALE					FEMALE				
	Total	G. Pos.	G. % Pos.	W. Pos.	W. % Pos.	Total	G. Pos.	G. % Pos.	W. Pos.	W. % Pos.
Dementia precox	293	46	15.69	37	12.62	149	21	14.09	18	12.08
Manic depressive	69	11	15.94	9	13.04	47	6	12.76	4	8.51
Senile psychosis	56	9	16.07	7	12.50	36	5	13.88	4	11.11
Imbecility	57	7	12.28	6	10.52	26	4	15.38	3	11.53
Epileptic psychosis	88	8	9.09	6	6.81	42	6	14.28	5	11.90
Melancholia involutional	0	0	00.00	0	00.00	56	6	10.71	4	7.14
Paresis	58	57	98.27	56	96.55	9	9	100.00	9	100.00
Alcoholic psychosis	26	3	11.53	2	7.68	22	5	22.72	3	13.63
Psychosis with brain lesion	17	4	23.52	3	17.64	40	8	20.00	5	12.50
Melancholia	7	0	00.00	0	00.00	0	0	00.00	0	00.00
Imbecility with psychosis	1	0	00.00	0	00.00	9	3	33.33	3	33.33
Depression—undifferentiated	2	0	00.00	0	00.00	9	4	44.44	3	33.33
Paranoia	7	1	14.28	1	14.28	5	0	00.00	0	00.00
Psychosis with cerebral sclerosis	2	0	00.00	0	00.00	4	2	50.00	2	50.00
Infective exhaustive psychosis	4	0	00.00	0	00.00	8	2	25.00	2	25.00
Alcoholic hallucinatory	11	5	45.45	3	27.27	3	0	00.00	0	00.00
Drug habitue	2	0	00.00	0	00.00	0	0	00.00	0	00.00
Gross brain lesion—post apoplectic	3	1	33.33	1	33.33	2	0	00.00	0	00.00
Dementia	4	1	25.00	1	25.00	3	0	00.00	0	00.00
Constitutional inferiority	6	1	16.66	0	00.00	2	0	00.00	0	00.00
Toxic psychosis	3	1	33.33	1	33.33	4	1	25.00	1	25.00

TABLE II—CONT'D

PSYCHOSIS BY SEX

	MALE					FEMALE				
	To-tal	G. Pos.	G % Pos.	W. Pos.	W. % Pos.	To-tal	G. Pos.	G. % Pos.	W. Pos.	W. % Pos.
Epileptic imbecile	4	0	00.00	0	00.00	0	0	00.00	0	00.00
Cerebral syphilis	5	5	100.00	4	80.00	7	7	100.00	5	71.42
Presenile delusional insanity	1	0	00.00	0	00.00	1	0	00.00	0	00.00
Gross brain lesion—arteriosclerosis	3	1	33.33	0	00.00	0	0	00.00	0	00.00
TOTAL	729	161	22.08	137	18.79	484	89	18.38	71	14.66

and negative Hecht-Weinberg-Gradwohl test, and two cases with two-plus Wassermann tests and negative Hecht-Weinberg-Gradwohl tests. Three of the number showed the same on repetition of the test, and the cases all had clinical symptoms of syphilis. In seven cases I found negative Wassermann reactions and four-plus Hecht-Weinberg-Gradwohl reactions, while previous Wassermanns showed negative reactions and the cases had no clinical history manifestations of syphilis.

The results of the Hecht-Weinberg-Gradwohl and Wassermann reactions for 1213 sera are, as follows: There were 250 positive Hecht-Weinberg-Gradwohl tests, or 20.61 per cent positives, and 208 positive Wassermann reactions, or 17.14 per cent positives. One hundred twelve cases showed four-plus Hecht-Weinberg-Gradwohl tests with the Wassermann tests showing one-, two-, and three-plus. In thirteen cases the Wassermann tests were negative and the Hecht-Weinberg-Gradwohl tests were four-plus, with eight of the thirteen showing a four-plus spinal fluid.

I am sure many of the cases that are doubtful will be cleared up by using the Hecht-Weinberg-Gradwohl test and in addition the Wassermann and spinal fluid. However, a doubtful test is of sufficient importance to demand a repetition.

In this hospital the diagnoses of the cases are not made by the assembled staff until all the data are procured, including the lab-

TABLE III

FURTHER ANALYSIS OF COMBINATION OF THE TESTS

PSYCHOSES	NUMBER OF TESTS	HECHT-GRAD-WOHL	WASSERMANN REACTION			
		Positive	+	++	+++	++++
Dementia precox	442	67	7	14	9	32
Manic depressive	116	17	4	3	2	8
Senile psychosis	92	14	3	3	3	5
Imbecility	83	11	1	2	2	5
Epileptic psychosis	130	14	0	2	3	6
Melancholia involutional	56	6	2	1	1	2
Paresis	67	66	1	5	9	51
Alcoholic psychosis	48	8	1	2	1	2
Psychosis with brain lesion	57	12	4	4	2	2
Melancholia	7	0	1	0	0	0
Imbecility with psychosis	10	3	0	1	1	1
Depression—undifferentiated	11	4	1	0	1	2
Paranoia	12	1	0	1	0	0
Psychosis with cerebral sclerosis	6	2	0	0	1	1
Infective exhaustive psychosis	12	2	0	0	1	1
Alcoholic hallucinatory	14	5	1	1	0	2
Drug habitue	2	0	0	0	0	0
Gross brain lesion—post apoplectic	5	1	0	0	0	1
Dementia	7	1	0	0	1	0
Constitutional inferiority	8	1	0	0	0	0
Toxic psychosis	7	2	0	1	0	1
Epileptic imbecile	4	0	0	0	0	0
Cerebral syphilis	12	12	3	2	4	3
Presenile delusional insanity	2	0	0	0	0	0
Gross brain lesion—arteriosclerosis	3	1	0	0	0	0
TOTAL	1213	250	29	42	41	125

oratory findings. The accurate number of cases in which the finding of a positive Wassermann in the blood has pointed a way to the correct diagnosis has not been determined, but it is certain that quite a number of cases have been cleared up by these tests.

CONCLUSION

1. The Hecht-Weinberg-Gradwohl test has been in my hands a

better control of the Wassermann than any of the other controls in use.

2. Thirteen cases showed a four-plus Hecht-Weinberg-Gradwohl with negative Wassermann reactions; and 29 cases with doubtful reactions and 83 cases with two-plus and three-plus Wassermann reactions.

3. All cases that showed a doubtful Wassermann reaction were cleared up by repetition of the test and using the Hecht-Weinberg-Gradwohl test.

4. Among the series of cases there were 93.3 per cent of sera which were found to contain sufficient complement and natural antihemolysin for the conduct of the Hecht-Weinberg-Gradwohl test. There were 11 cases which were diagnosed clinically as syphilis and gave a Wassermann reaction and Hecht-Weinberg-Gradwohl reaction both negative. Eight cases gave positive Wassermann tests with negative Hecht-Weinberg-Gradwohl tests and seven cases gave negative Wassermann tests and four-plus Hecht-Weinberg-Gradwohl tests from which syphilis could be excluded.

5. Among the paretics of this series the Hecht-Weinberg-Gradwohl was positive in 98.5 per cent of the cases and the Wassermann was positive in 97.01 per cent of the cases.

The statistics here presented give evidence of the great practical importance of using the Hecht-Weinberg-Gradwohl reaction in connection with the Wassermann reaction among the insane, and the extra amount of labor consumed is more than compensated by the amount of information obtainable.

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A PRELIMINARY REPORT ON SYPHILITIC AND ARSENICAL JAUNDICE*

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JAUNDICE occurring in the course of an attack of syphilis may be largely divided into two groups: first, the jaundice that occurs in untreated cases of syphilis and which is due to an invasion of the liver by the Treponema pallidum, and second, that which occurs during or subsequent to the treatment of the syphilis by salvarsan, or its substitutes, and which may be due to the organism, the drug or a combination of both. The incidence of the first type is not great. Osler[1] states that in eighteen years in Johns Hopkins Hospital there were thirty cases diagnosed during life. Fifty-five cases were found in 2,500 autopsies of all classes. In the Philadelphia Hospital out of 5,088 autopsies of all classes there were 188 cases of syphilis of the liver. At St. George's Hospital out of 11,629 autopsies of all classes there were 64 that showed hepatic involvement. He states that jaundice occurs in generalized syphilis in 0.37 per cent of cases. McNeil[2] finds that 64 cases of syphilis of the liver were diagnosed during life in 1,200 cases of syphilis. Out of 300 autopsies on syphilitic persons he found 90 with hepatic syphilis. Lockhart[3] reports two cases of jaundice occurring in generalized syphilis in considerably over a thousand cases of syphilis he has treated in the last year. In 2,243 patients treated for syphilis at this hospital in the last fourteen months we have found two cases which showed unmistakable evidence of belonging to the first group.

In the second group the incidence is somewhat greater. Harrison[4] states that jaundice occurs in 0.6 per cent of cases of syphilis during or subsequent to treatment with arsenical preparations. Wadia[5] reports one fatal case but does not state the total number of cases treated. McDonagh[6] reports two cases treated with the original salvarsan. In his cases, which he considers are due to the toxic action of the drug, he found that the poisoning had produced a cure of the syphilis. Morgan,[7] quoting Ravaut, says that in 94,762 injections of arsenical preparations in the treatment of syphilis in the French Army, in which the following preparations were used, novarsenobillon 37,352, neosalvarsan 35,826, salvarsan and arsenobillon 9,215, galyl 8,846 and luargol 3,523, there were twenty cases of jaundice which were divided among the various drugs as 7, 8, 1, 2, and 2, respectively. Sanes and Kahn[8] quote Severin and Hemichsdorf who cite two cases. They also quote Janeway who reports one case. They themselves report one case. Fenwick, Sweet and Lowe[9] report two fatal cases out of 263 cases of syphilis treated by them. These authors quote a personal communication from McKenna, who had no cases among the great number of cases of syphilis that he had treated. Langevin and Brulc[10] report two cases in 248 cases of syphilis that they had treated. They decide that these cases were entirely due to the syphilis. Bawden[11] in 500 cases of syphilis reports one case of jaundice. Hanington[12] reports two cases. Harrison[13] states that in the last 2¼ years he has had only six cases occur in the Syphilis Clinic at the Military Hospital, Rochester Row, London. Milian[14] reports two cases in the course of treatment with neosalvarsan. Klausner[15] and Lube[16] each report two cases. Lockhart[17] reports one case occurring after the third injection of novarsenobillon. McTaggart[18] reports eleven cases occurring at a variable interval after completion of their course of treatment for syphilis. None of these cases was fatal. In the Syphilitic Clinic of this hospital among 2,243 cases of syphilis treated with 13,664 injections of various arsenical preparations there were 39 cases belonging to this group.

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The classification of syphilis of the liver, as given by Osler, may be subdivided into three groups: *First,* syphilitic jaundice which occurs in the stage of generalization. It usually appears suddenly in cases of florid syphilis, with a pronounced rash, and lasts five to six weeks. The liver and spleen are not enlarged and the stools are not clay colored. The pathology of this condition is not well understood, but there are four theories. It may be due to duodenal catarrh, to the pressure of enlarged lymphatic glands on the bile ducts, to affections of the blood vessels of the portal canals or to catarrh of the small bile ducts. Osler considers this latter the most probable. *Second,* acute necrotic hepatitis, which may be general, and result in acute yellow atrophy or focal. *Third,* late conditions, such as gummata, gummatous cicatrices, perihepatitis, cirrhosis or thrombosis in the hepatic veins.

It is with Class 1 and Class 2 that we intend to deal in this section of the subject. Late conditions are not of frequent occurrence among soldiers who are mostly young men and whose syphilis is recent. The exact pathology of the icterus of generalized syphilis has not yet been determined. McNeil[2] in one autopsy of his series of 7 cases of early syphilitic hepatitis of which four had jaundice, found an acute hepatitis and cholangitis. The liver parenchyma was infiltrated with small round cells and there were a few giant cells. There was proliferation of the fibroblasts. In his cases the liver was enlarged and tender, there was jaundice which he did not consider to be obstructive, there were gastric symptoms and two cases had fever. The longest period before relief was obtained was two weeks. McDonagh[6] states that cholangitis is the commonest liver condition in early syphilis. Hutchinson[19] considers early syphilitic jaundice to be of a catarrhal nature. He says the liver is tender on pressure and quotes Lancereaux, who believes it to be due to general congestion of the liver. Langevin and Brule[10] discuss the condition at considerable length. They quote Gubler who believes it to be due to an internal roseola of the bile ducts. They say that it is generally believed to be due to an inflammatory obstruction of the large or small biliary canals. In opposition to this they quote Gaucher and Drioux who claim that it is a hemolytic jaundice, as there is no evidence of syphilitic involvement of the ducts, but that it is not likely the majority of cases are of this type. They differ from Widal and Abrami that the icterus is due to destruction of large numbers of the red blood cells, for they claim that in these cases there is not sufficient anemia to produce the condition. It does not, however, seem to them to be angiocholitic. They agree with Chaffaurd who compares it with secondary syphilitic nephritis and calls it a true precocious syphilitic hepatitis. Arguing on an analogy of Weil's disease in which the bile ducts are normal but the lobules are crowded with spirochetes, they say it is reasonable to suppose that the same is the case in syphilis. They consider the jaundice to be due to retention caused by damage to the liver cells themselves by the Treponema pallidum. They advance four reasons why they believe it to be hepatic and not angiocholitic. It occurs frequently in alcoholics who have damaged liver cells. The feces are bile stained. There is a dissociation of bile substance in the urine. The rate of disappearance of the jaundice is slow. They quote Lemiere who states that the biliary retention of the dissociated type can not evidently be attributed to an obliterating lesion of the biliary canal, large or small, for in such case the retention would bear equally upon the pigments and the salts. The isolated retention of the pigments or of the salts alone can only be explained by the involvement of the hepatic cells themselves, which are alone capable of such selection of the constituent elements of the bile. In their two cases they prove that this dissociation of the bile substances in the urine exists.

In the second group of cases of jaundice the problem of the pathologic condition existing is more difficult still. The action of syphilis, the action of the arsenical preparations, the action of mercury, or the action of a combination of these has to be considered. From the preceding paragraphs the consensus of present-day opinion seems to be that jaundice occurring in generalized syphilis is due to the action of the toxins of the Treponema pallidum on the liver cells. Arsenic and mercury both act upon the same part of the organ. We do not consider that mercury enters largely into the question. Neither the symptoms of the jaundice itself nor any sign occurring during the course of the treatment that would indicate intolerance to mercury point to this drug being a causative factor. The pathologic lesions moreover are not those of mercurial poisoning. Whether the new organic arsenical compounds act as a whole or by virtue of their contained arsenic is at present a disputed point. There are two theories advanced to account for the toxicity of these substances. Sollmann[20] considers that their action is due to the contained arsenic. He considers that the difference between organic and inorganic compounds of arsenic is mainly a quantitative one. He states that arsenical compounds relax the capillaries, increase their permeability and so produce fatty degeneration of the cells. The action on the cells is probably due to the fact that arsenic hinders protoplasmic oxidation. In chronic poisoning with arsenic there is fatty degeneration of the liver cells akin to that produced by phosphorus, and he quotes Ullmann who states that this degeneration occurs around the central vein of the liver lobule after intravenous injection. He advances the theory that in chronic arsenical poisoning the increased size of the fatty liver may cause pressure on the bile ducts and so produce icterus. On the other hand McDonagh[21, 6] considers that the new organic preparations act by their oxidizing power. He states that arsenic passes through the body unchanged, being trivalent when administered and trivalent when excreted. To his mind its only action is that of a catalytic agent. He considers that the toxicity is due to either an increase of the hydrogen-ion concentration or to an increase of the hydrogen in the blood. Organic arsenical preparations make the blood too acid and are therefore toxic. The general opinion, however, is that it is the contained arsenic that gives the organic arsenical preparations their toxicity.

There is some diversity of opinion as to the pathology of jaundice occurring during the treatment of syphilis with organic arsenical preparations. Harrison[4] considers that it is due to an obstruction of the common duct by an inflamed duodenal mucous membrane. In one case which he autopsied there was inflammation of the duodenum, with no particular degeneration of the liver cells. In the late fatal cases he[13] finds great degeneration of the liver, but he considers these cases due to some unknown agent introduced at the same time with the arsenical preparation. Wadia[5] found acute degenerative changes in the liver cells. Severin and Hemischdorf quoted by Sanes and Kahn[8] report that there were degenerative changes in the liver, in one case resembling syphilis and in the other arsenical poisoning. In Fenwick, Sweet and Lowe's[9] two cases they found two areas in the liver, one green and the other red. In the green area there was a cirrhosis of the multilobular type of recent standing. The young fibrous tissue was infiltrated with small round cells. The hepatic cells showed degeneration with fatty infiltration. There was a catarrhal cholangitis of the larger bile ducts. In the red part there was coarse cirrhosis. The cells were completely degenerated and the bile ducts were better preserved. The color was due to extravasation of the red blood cells in the center of the lobules, the periphery being free. The cirrhosis was not considered to be syphilitic. Warthin[22] cites one case of syphilis dying of salvarsan poisoning in which there were areas of focal necrosis containing the Treponema pallidum throughout the liver. In our one fatal case, which will be considered at greater length below, the main pathologic lesion found was degeneration of the cells surrounding the central vein.

To sum up the pathologic findings in these cases it would seem that the condition is a diffuse intralobular hepatitis. Though the degeneration of the liver cells is the principal lesion, there also may be found degeneration of the portal canals, of the small bile ducts, and some replacement with fibrous tissue. Harrison's theory of duodenal catarrh can not be held in the face of these general pathologic and the urinary and the fecal findings. Brown, quoted by Sanes and Kahn,[8] from experimental work on animals, classifies the lesions of the liver due to arsenic as follows: (1) Diffuse, which may be either general or focal and may appear in widely distributed necrosis of individual cells. (2) Degeneration and necrosis may occur in the central zone. The degeneration is usually fatty in character and is the same as occurs with large doses of other chemicals. (3) The degeneration may occur in the portal spaces and periphery of the lobules. In small doses the bile ducts receive the greatest injury and there is slight fatty degeneration of the peripheral cells. It would appear that the pathologic condition which gives rise to the icterus occurring during the treatment with organic arsenical compounds is that which is found in early syphilitic jaundice and is also found in poisoning by large doses of arsenical compounds. It would seem, therefore, that the causative factor may be either the toxins produced by the Treponema pallidum, the arsenical preparations, or a combination of the two. We consider the latter the most probable. The liver damaged by the treponemal toxins is unable to handle the arsenical compounds and the degenerated cells are rendered more susceptible to the toxic action of the arsenic.

Jaundice occurring in early syphilis is then capable of classification into three types.

Type A. Diffuse syphilitic hepatitis. These cases develop the icterus during the stage of generalization, at some shorter or longer period after the appearance of the primary sores, and before the case has been placed on treatment.

Type B. Diffuse syphilitic hepatitis, in which the symptoms are elicited by the provocative action of the early injections of the arsenical preparations. These cases after the first, second or third injection develop icterus. The liver is probably swarming with the Treponema pallidum. The first injection destroys a large number of the organisms and the liberated toxins cause degenerative changes to take place in the liver cells. There is a time interval required for this action to produce clinical evidences, and so the symptoms may not appear for from 24 hours to three weeks after the first injection of the arsenical compound.

Type C (a). Early arsenical jaundice. In this type of case there is probably a mild syphilitic hepatitis but there are not sufficient Treponema pallidum present to have the Herxheimer reaction that produces Type B. called forth. The liver cells receive such damage, however, from the treponemal toxins that they can not cope with the added toxicity due to the arsenical compounds and so the cells themselves become degenerated. In this type the icterus appears subsequent to the fourth and previous to the final injection of the arsenical compound.

Type C (b). Late arsenical jaundice. In this type the causative factor is much the same as in the preceding, but the syphilitic hepatitis is probably milder, and indeed need not be present if there is sufficient history of alcoholism or some other condition which has caused damage to the liver cells and thus increased their susceptibility to the action of the arsenic.

Our reasons for making this classification and our differential diagnosis between the three types will be cited later.

CLASS A. JAUNDICE OCCURRING DURING GENERALIZED SYPHILIS

In our series of 42 cases we had 2 cases of this type. Both were in young men, twenty-one years of age. There was no family or personal history that would point towards a previously damaged liver. They were both mildly alcoholic, but not more so than the average soldier. They were both admitted with clinically generalized syphilis, in the one case the type was florid showing a marked involvement of the skin and mucous membranes. The Wassermann was strongly positive. In the other case the patient had a markedly indurated typical primary and had general glandular enlargement. The icterus appeared six days after the appearance of the sore. The Wassermann was negative. Jackson[23] has proved that syphilis is generalized about the same time that the primary sore appears and it is known that the Wassermann reaction does not become positive for some weeks after this. This case was clinically early generalized or late primary syphilis and the icterus was unquestionably syphilitic. The prodromal symptoms were slight in the first case consisting of mild gastric disturbances with loss of appetite and nausea. There was some pruritus before the patient noticed the yellow color appearing. These prodromal symptoms were of only short duration. The second case had no prodromal symptoms and the icterus was not marked until the morning after the first injection of novarsenobillon. In Case 1 the entire skin, mucous membranes and conjunctivæ were of a pronounced yellow tint. At no time was the liver or spleen enlarged. The blood coagulation time was not increased. In Case 2 the conjunctivæ and palate were alone colored, the tint being faint yellow. The liver was slightly enlarged and the spleen palpable. In both cases there was a heart murmur which disappeared under antisyphilitic treatment. The stools were normal in color at all times. The 24-hour sample of urine was normal in amount, reaction and specific gravity. There was no albumin or sugar but bile salts were markedly present. The duration of the jaundice, reckoned until the time that no bile salts were found in the urine, was in Case 1, 38 days, and in Case 2, 15 days. Both cases were placed on carefully graduated courses of novarsenobillon and mercury and were closely watched. During the treatment the first case continued to show gastric disturbances, but the second had no symptoms whatever. There was no reaction after any of the injections of novarsenobillon. The icterus faded slowly. The Wassermann at the end of the first course in Case 1 was still positive and he was placed on a recurrent course and discharged from hospital as an out-patient. At that time there was no sign of jaundice apparent and he felt well. In Case 2 the Wassermann was negative on the completion of the course and on discharge from hospital there was apparently complete recovery.

CLASS B. SYPHILITIC JAUNDICE ELICITED BY THE HERXHEIMER REACTION

There were six cases in this class. They were all young men, their ages varying from twenty-one to twenty-six. In none of the cases was there any family or personal history that would indicate previous liver involvement. Four of them did not use alcohol and the other two were extremely moderate drinkers. Four of the cases were clinically primary syphilis and the other two were early generalized. The Wassermann taken before treatment commenced was in every case negative. In one case the time between the appearance of the primary sore and admission to hospital was twenty-eight days, so that this was probably verging on signs of early generalization. In

Table of Organic Arsenical Compounds Used in the Antisyphilitic Treatment of These Cases*

NO.	STAGE OF SYPHILIS	ALBUMIN IN URINE DURING TREATMENT	ARSENICAL PREPARATION	NO. OF INJECTIONS	TOTAL DOSAGE	NO. OF DAYS BETWEEN LAST INJECTION AND APPEARANCE OF ICTERUS	WASSERMANN AFTER ICTERUS HAS SUBSIDED
			Type B. Jaundice Provoked by the Herxheimer Reaction				
1	Primary	Negative	Novarsenobillon	4	1.95 gm.	1 day	Negative
2	Generalized	Negative	Novarsenobillon	3	1.35 gm.	7 days	Negative
3	Primary	Negative	Novarsenobillon	2	0.90 gm.	3 days	Unknown
4	Primary	Negative	Novarsenobillon	2	0.90 gm.	1 day	Unknown
5	Generalized	Negative	Novarsenobillon	2	0.90 gm.	5 days	Negative
6	Primary	Negative	Novarsenobillon	1	0.45 gm.	4 days	Unknown
			Type C (a). Early Combined Syphilitic and Arsenical Jaundice				
1	Primary	Negative	Novarsenobillon	9	5.45 gm.		
			Galyl	1	0.4 gm.		
			Diarsenol	1	0.50 gm.	3 days	Negative
2	Generalized	Negative	Novarsenobillon	6	3.00 gm.	5 days	Negative
3	Primary	Negative	Novarsenobillon	4	2.55 gm.		
			Diarsenol	2	0.60 gm.	3 days	Strongly positive
4	Primary	Negative	Novarsenobillon	9	5.30 gm.	12 days	Positive
5	Generalized	Negative	Unknown (Given 8 months previous to admission)	7	Unknown		
			Novarsenobillon	10	5.85 gm.	6 days	Strongly positive
6	Primary	Negative	Arsenobillon	3	0.90 gm.		
			Novarsenobillon	3	2.25 gm.	2 days	Negative
7	Late	Negative	Novarsenobillon	10	4.95 gm.	10 days	Negative
8	Generalized	Negative	Novarsenobillon	8	4.50 gm.	3 days	Unknown
9	Generalized	Negative	Unknown	7	Unknown		
			Novarsenobillon	3	1.50 gm.	1 day	Unknown
10	Late	Negative	Arsenobillon	5	1.80 gm.		
			Novarsenobillon	6	4.20 gm.	1 day	Strongly positive
11	Generalized	Negative	Novarsenobillon	9	5.25 gm.	2 days	Unknown

Type C (b). Late Combined Syphilitic and Arsenical Jaundice

1	Generalized	Negative	Novarsenobillon	7 (1½ yrs. ago)	4.20 gm.		
			Novarsenobillon	7	4.20 gm.	25 days	Strongly positive
2	Primary	Negative	Novarsenobillon	11	6.80 gm.	67 days	Negative
3	Late	Negative	Novarsenobillon	6	3.30 gm.	34 days	Negative
4	Generalized	Negative	Novarsenobillon	7	4.20 gm.	58 days	Strongly positive
5	Primary	Negative	Novarsenobillon	7	4.20 gm.	74 days	Negative
6	Generalized	Negative	Salvarsan (1915)	6	Unknown		
			Neosalvarsan (1915)	3	Unknown		
			Novarsenobillon	4	2.60 gm.	132 days	Negative
7	Congenital	Negative	Diarsenol	3	0.90 gm.		
			Novarsenobillon	8	5.45 gm.	33 days	Positive
8	Generalized	Negative	Novarsenobillon	9	5.50 gm.		
			Galyl	1	0.40 gm.		
			Diarsenol	1	0.30 gm.	54 days	Negative
9	Primary	Negative	Novarsenobillon	7	4.20 gm.	95 days	Negative
10	Generalized	Negative	Diarsenol	7	2.70 gm.	57 days	Negative
11	Late	Negative	Novarsenobillon	9	4.85 gm.		
			Diarsenol	2	0.60 gm.	22 days	Positive
12	Primary	Negative	Novarsenobillon	7	4.20 gm.	48 days	Negative
13	Generalized	Negative	Novarsenobillon	7	4.20 gm.	58 days	Negative
14	Generalized	Negative	Novarsenobillon	7	4.20 gm.	82 days	Negative
15	Generalized	Negative	Novarsenobillon	9	5.70 gm.		
			Diarsenol	2	0.80 gm.	97 days	Negative
16	Primary	Unknown	Unknown	3	Unknown		
			Novarsenobillon	3	Unknown	103 days	Negative
17	Primary	Unknown	Unknown	7	Unknown	59 days	Negative
18	Congenital	Negative	Novarsenobillon	11	4.95 gm.	83 days	Strongly positive
19	Primary	Negative	Novarsenobillon	8	4.95 gm.	79 days	Negative
20	Primary	Negative	Novarsenobillon	8	4.95 gm.	59 days	Unknown
21	Generalized	Negative	Unknown (1916)	8	Unknown		
			Unknown (1917)	7	Unknown		
			Unknown (1918)	6	Unknown	58 days	Unknown

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*Explanatory Note on Table.—The treatment of syphilis as laid down by the War Office for the British and Canadian Armies consists of a course of seven injections covering a period of 56 days. If salvarsan substitutes are used the total dosage is 2.8 grams. If neosalvarsan substitutes are used the total dosage is 4.2 grams. Should this course not produce a negative Wassermann a recurrent course is given consisting of four injections totalling for salvarsan substitutes 1.8 grams, for neosalvarsan substitutes 2.7 grams. This total dosage is the ordinary one used at this hospital. The preparation usually used in the Canadian Army is novarsenobillon or arsenobillon. In the British Army the preparation usually used is Kharsivan. In the cases in which the preparation is marked unknown in the table the probable total dosage can be gathered from these facts.

the other three primary cases the time was much shorter, being four, three and two days respectively. For the arsenical preparations used in this type and the succeeding type the accompanying table should be consulted. While under treatment previous to the development of the icterus two of the cases showed reactions after receiving their injections, the others did not. The reactions experienced by the two cases were, in the one instance mild, being simply that the patient during the second injection could taste and smell the drug, and in the other instance more severe, the drug being tasted and smelt during both injections and followed both times by headache, nausea, and vomiting. A prodromal period was present in four of the cases varying in length from three to ten days. In two cases the preicteric symptoms were severe, in one commencing with a rise of temperature to 101° and mild dermatitis; three days later the jaundice appeared. In the second case the patient developed chills, nausea, and vomiting. There were severe pains in the legs and back and tenderness over the posterior cervical glands. Frontal headaches were also pronounced. The temperature rose to 104.5°. These symptoms persisted for five days before the icterus appeared. The prodromal symptoms in the other cases were milder, consisting of slight chills, nausea, vomiting and general pains. The period of icterus averaged 40 days, varying from 15 to 65. In two cases there were no symptoms and in one case they consisted of only a feeling of general malaise. In two cases they consisted of loss of appetite, headache, vomiting, weakness and one of the two had marked pruritus. In one case the symptoms were severe, headache, weakness, neuromuscular pains, nausea, anorexia and aching pains in the bones particularly in legs. In two cases there was abdominal tenderness located in the epigastrium. There was increased rigidity of the abdominal muscles on the right side in one case. The liver and spleen could only be found enlarged in one case and the enlargement of both organs was slight. At no time was the liver more than one inch below the costal margin in the nipple line. The tint in three cases was pronounced, being an intense yellow and in the other three it was much slighter. The stools varied from light brown to whitish yellow. The more pronounced the icterus the less color did the stool contain, but bile pigments were invariably present. The urinary findings were negative except for the presence of bile. The amount, however, of the 24-hour sample was small at first, increasing as the jaundice disappeared. The temperature, pulse, and respirations were in every case normal though at the commencement of the icterus there was a slight slowing of the pulse, but not below 60. All cases made a good recovery.

CLASS C (a). EARLY COMBINED SYPHILITIC AND ARSENICAL JAUNDICE

There were eleven cases of this type, the ages ranging from twenty-two to forty-one and in all cases the family history was negative for any cause of liver involvement. The personal history showed no case with a previously affected liver. All were moderately alcoholic, but in no case to a marked excess. Four cases were primary before treatment was commenced, five were generalized and two were late. In one case the initial Wassermann was negative; this case was primary. The period between the last injection of the organic arsenical compound and the appearance of the icterus varied from one to twelve days. Five cases showed reactions after their arsenical injections consisting of the patient tasting and smelling the drug during the injection and nausea, vomiting and headache within the first twenty-four hours. In one case there was an urticarial eruption. Prodromal symptoms were present in five cases with mild symptoms consisting of gastric disturbances, headache, pains in stomach and slight constipation. In the other cases there were no prodromal symptoms. The length of prodromal period averaged 18.25 days, varying from 5 to 31 days. Three cases showed symptoms during the period of icterus, these being mild and consisting of gastric disturbances, pains in stomach, headache and general malaise. The color was light yellow and in most cases was slight. This is probably due to the fact that these patients were in hospital under treatment and so could be observed. The heart and lungs were normal in every case, in two cases the liver was enlarged, but in neither of these was it more than one inch below the costal margin. In one case the liver was small. The edge in all cases was smooth. In one case the spleen was palpable and in one case there was tenderness over the gall bladder and in one over the spleen. The feces were in no instance clay colord but varied from a yellowish brown to a dark brown. The urinary findings were negative except for the presence of bile and the increase in amount noted in the previous type. The blood count was normal. In only one case did the temperature rise above 99 throughout the course of the disease. The pulse was never lower than 60. This was in the early period of the jaundice and it rose gradually to normal as the icterus disappeared. The respirations varied early in the course of the disease between 22 and 20 and gradually decreased to normal with the disappearance of the color. The duration of the jaundice varied from 4 days to 122 days. All cases made a good recovery.

CLASS C (b). LATE COMBINED SYPHILITIC AND ARSENICAL JAUNDICE

There were 22 cases in Class C (b). Their ages ranged from 19 to 43. With the exception of two cases of congenital syphilis the family histories were negative. Two cases gave a history of jaundice occurring a number of years ago; three cases gave a history of indigestion extending over a considerable period of time, and one case had lived in the tropics, though there was no history of jaundice or any tropical disease. Seven cases were primary syphilis when the original treatment was commenced. Nine were generalized, 2 were late and 2 were congenital. In two cases it was impossible to ascertain the condition at that time, but they were thought to be primary. Four cases gave a negative Wassermann at the commencement of treatment. In no case during treatment, so far as can be ascertained, or prior to the development of the icterus, was there any albumin in the urine or any signs or symptoms of renal involvement. The shortest period between the last injection of the arsenical compound and the development of the icterus was 22 days, the longest was 132 days. Fourteen cases showed prodromal symptoms which consisted of loss of appetite, gastric disturbances, cramp in the epigastrium, general malaise, persistent headache, pains in the knees and ankles and constipation, though the latter only occurred in a few cases. One case developed dermatitis, and two days later the icterus occurred. In five cases there were no prodromal symptoms. The shortest prodromal period was 2 days and the longest 19 days. During the course of the icterus 14 cases showed symptoms which were much the same as those of the prodromal period, consisting of general malaise, weakness, loss of appetite, nausea, vomiting, epigastric pains, pain over the liver region, flatulence, neuromuscular pains, in some cases constipation and in a few cases itching of the skin, heartburn and sour stomach were also complained of. In 7 cases there were no symptoms. The skin, mucous membranes and conjunctivæ were yellow in color and in all but three cases the tint was marked. Examination of the heart and lungs was negative in every case. Six cases showed enlargement of the liver, the lower border varying from one inch below the costal margin in the nipple line to two and one-half inches below. In every case the edge was smooth. In three cases there was tenderness over the margin of the liver and the gall bladder. In four cases the spleen could be felt and in one case there was tenderness on palpating it. In only one case was there epigastric tenderness. Twelve cases gave a negative physical examination. The feces varied from a whitish yellow to a dark brown, but in all cases bile was present. The urinary findings were much the same as in the previous type. The temperature, pulse, and respirations resembled Class C (a) also. In one case there was a leukocytosis and in one case there was a low red blood count. The differential count was normal. A third of the cases gave a history of reactions after the arsenical injections. In one case the temperature after the first injection rose to 105°. In the majority of the cases with reactions the signs were those of intolerance, the patient could taste and smell the drug during the injection, and towards the end of his course developed nausea, vomiting, and loss of appetite in the twenty-four hours following its administration. Three of the patients gave a history of being nonalcoholic. The duration of the icterus varied from 7 days to 101 days, averaging 26.4 days. All cases went on to recovery except one which was fatal. In one case there was a slight relapse of the gastric symptoms, but none of the jaundice. In the one fatal case the history was as follows:

Private C., age 23, family and personal history negative. In October, 1916, he contracted syphilis and received three intravenous injections of some arsenical preparation and four intramuscular injections of mercury. At the end of this course his Wassermann was negative. In November, 1917, his condition being clinically generalized, he received seven intravenous injections of an arsenical compound and eight intramuscular injections of mercury followed by two weeks of potassium iodide. His Wassermann being then positive, he received three intramuscular injections of some arsenical preparation and three of mercury. He was discharged from hospital on February 4, 1918. About March 12 he reported to this hospital, his Wassermann being positive, and was placed on a three months' course of mercury and potassium iodide. (For the arsenical preparation and the total dosage the explanatory note to the Table should be consulted.) On March 15 he was transferred to the staff of this hospital and on the same day he arrived complained of severe gastric disturbances. He was examined, found to have jaundice, and admitted.

Examination on admission revealed the following symptoms: Patient complains of nausea, which is continuous, of vomiting and epigastric pains. There is marked icterus of the skin, mucous membranes, and conjunctivæ, the color being a pronounced yellow. The tongue is coated, the heart and lungs appear normal, the liver is not enlarged, the spleen is enlarged, the border being 2½ inches below the costal margin. There is some epigastric tenderness. The temperature is 97.4°, pulse 68, and respirations 18. Urinalysis. Amount 1100 c.c. Color dark amber. Reaction acid. Specific gravity 1.010. Albumin negative. Sugar negative. A few granular casts present. Bile salts present in large amounts. Arsenic absent. The nausea and vomiting continued and were practically uncontrollable. The jaundice increased daily. On the twenty-fifth the spleen was about the same size, the liver, however, was definitely smaller than normal. A blood culture was negative. There was no leukocytosis. Urinalysis. Amount 730 c.c. Color dark amber. Reaction acid. Specific gravity 1:016. Albumin positive. Sugar negative. Bile salts markedly present. Granular casts present. From this date the patient sank into a comatose state. Urinalysis on the twenty-ninth. Amount 330 c.c. Color dark amber. Reaction acid. Specific gravity 1.022. Albumin definitely present. Sugar negative. A large amount of bile salts and a large number of granular casts present. On the thirtieth the patient died.

Autopsy Findings.—Macroscopic. There was a deep yellow tint over the entire body. The conjunctivæ were stained yellow. There was a small amount of subcutaneous fat. The cartilages of the ribs were stained yellow. The peritoneal fluid was increased in amount, brownish in color and clear. The left cupola of the diaphragm was at the level of the fifth rib, the right at the fourth interspace. The lower margin of the liver was two fingerbreadths above the costal margin in the nipple line, in the midline it was two fingerbreadths below the ensiform cartilage. The pleural and pericardial fluids were bile stained as was also the endocardium. Multiple atheromatous patches were present in the aorta. The lungs and bronchial glands were normal. The spleen was soft. The duodenum showed no obstruction to the flow of bile. The glands around the foramen of Winslow were enlarged. The liver was small, weighing only 34½ ounces. It was soft and had a mottled yellow color. The cut surface was yellow in color and the central veins were prominent. The gall bladder contained a small amount of yellowish mucoid fluid, the mucous membrane was normal. The suprarenals were soft and their medulla was pale. The kidneys were enlarged, soft, and weighed 6½ ounces apiece. The capsule stripped easily. The cut surface was pale and bile stained, the cortex was granular and the striations were difficult to make out and crooked. The digestive tract was normal. The pancreas was normal.

Microscopical.—

Heart. The muscle cells were fragmented.

Lungs. There were hemorrhages in some areas. In the alveoli and in the outer zones of the hemorrhagic areas there were collections of small round cells.

Liver. The central and mid-zone of the lobules were completely degenerated. The fibrous tissue framework outlined the position of the original liver cord.

The spaces in the connective tissue framework were occupied by small round cells, pigment, and debris. In the outer zone of the lobule a few islands of liver cells were still recognizable. The bile ducts were intact.

Spleen. There was considerable bile pigment deposited in the areas between the lymphoid nodules. There was infiltration with small round cells.

Kidney. These organs showed marked vacuolation, disintegration and bile staining of the epithelial cytoplasm.

At present we are not prepared to make a complete report on the blood, urinary, and fecal findings, but we hope to do so in a later article. Suffice it to say that we agree with Langevin and Brule[10] that there is a dissociation of the constituents of the bile as excreted by the urine. The toxic action of the arsenical preparations, though injurious to the liver cells, already damaged by the toxins elaborated by the Treponema pallidum does not exert a greater lethal action against the syphilitic organism than ordinarily, for, in many cases the Wassermann is still positive at some interval after the subsidence of the icterus.

The consensus of opinion from the recent literature is that the probable pathology of *these conditions is a diffuse intralobular hepatitis* and from our observations we consider this to be correct. That the icterus is not obstructive is proved by the presence of bile in the stool, by the dissociation of the biliary substances as excreted in the urine, and by the slow disappearance of the jaundice. In the case of obstructive jaundice the latter would be rapid as soon as the obstruction had been removed. These three findings serve to differentiate this condition from any type of obstructive jaundice, whether the obstruction is present at the ampulla of Vater and due to duodenal catarrh, or in the large or small bile ducts, whether catarrhal in nature or otherwise. The primary causative factor is in all types syphilis, though in the late arsenical cases any previous condition that has resulted in permanent injury to the liver cells may supply the place that is usually taken by the toxins developed by the Treponema pallidum. In the case of syphilitic jaundice the liver is probably swarming with organisms and their toxins produce the damage to the liver cells. This class of case is considered to be syphilitic for the following reasons: It occurs in cases of generalized syphilis, there are usually other signs of early visceral syphilis present, and the icterus disappears under antisyphilitic treatment. One case in our series links this type with the next type—jaundice provoked by the Herxheimer reaction—very closely. In this case, though the icterus was present on admission, it was greatly increased the morning following the first arsenical injection. The liver in these cases is invaded by the Treponema pallidum though as yet not sufficiently to produce symptoms. The initial dose of the drug destroys a great number of organisms, and their toxic products in the liver produce degeneration of the liver cells and precipitate symptoms. We consider these cases to be syphilitic jaundice and not jaundice due to the arsenical preparation, whether acting on a previously damaged liver or not, for several reasons: First, the early appearance of the jaundice, namely, before the fourth dose of the drug, when only 1.35 grams of the preparation containing 0.27 gms. of arsenic had been administered. This is hardly enough to produce the symptoms seen in these cases. Second, the fact that these cases show no improvement when treated with intramine. *Intramine is a specific for poisoning with metallic substances.* In cases of the next class treated by this preparation the disappearance of the icterus is rapid. In the case of Class B whether given intramine or not the duration was much longer. We have not used this drug in a sufficiently large number of cases to make a complete report, but we hope to confirm this statement by statistics in a later communication. Though these cases are unquestionably syphilitic, there is one case among them that links them with the jaundice due to combined syphilis and arsenic, namely, the case in which dermatitis developed previous to the jaundice. In this case there was probably a great susceptibility to the toxic action of the arsenical preparation, but the condition of the liver and that of the skin are not necessarily associated. In Type C (a) that is, in those cases classified as early combined syphilitic and arsenical jaundice, the liver has received a less severe poisoning with the toxins of the Treponema pallidum than in the two former types but more so than in the late combined cases. The degenerated liver cells are rendered more susceptible to the arsenical intoxication, so that the causative factor is primarily syphilis, on which is superimposed the toxic action of the arsenical preparation. This is applicable to both early and late combined syphilitic and arsenical jaundice. In the early cases the syphilis is more severe and less arsenic is tolerated; in the late cases the syphilis is milder and the action of the arsenic slower. It does not seem necessary to attribute the condition in Class C to a hypothetic agent introduced with the drug as the lesions found in experimental work with arsenical preparations on animals and the pathologic findings in cases of early syphilis of the liver are sufficient to point to these two conditions as being the causative factors.

For the treatment of these conditions we would advise in the case of syphilitic jaundice appearing before treatment is commenced inaugurating the treatment by the use of mercury and potassium iodide for two weeks, the former being given intravenously in order that the syphilis may be controlled as quickly as possible. At the end of the two weeks an arsenical preparation may be given in small carefully graduated doses. Signs of intolerance, such as the patient perceiving the taste and smell of the drug during its administration, reactions with nausea and vomiting or a rise of temperature, or an increase of the jaundice should be carefully watched for and at the first appearance of any of these signs, intramine 3 c.c. should be administered intramuscularly.

In the case of the jaundice elicited by the Herxheimer reaction it is difficult to state what line of treatment should be followed. This type of case makes one think that it might be better to commence the treatment of all cases of syphilis with mercury in order to avoid the occurrence of this unpleasant complication. This, however, is not the ideal plan. Particular attention should be devoted to observing the condition of the liver in every case of syphilis whether primary, generalized or late. The initial dose of an arsenical preparation in all cases should be small in order to avoid the jaundice which may be provoked by the first injection. When the icterus has developed, the patient should receive the routine treatment of rest in bed, free catharsis and milk diet. He should be placed on mercury and potassium iodide and when signs of jaundice have been absent for a month he may recommence careful arsenical treatment, being watched for the reappearance of bile in the urine or any sign of arsenical intolerance.

To prevent combined syphilitic and arsenical jaundice every case of syphilis under treatment should be closely observed for any sign of intolerance to arsenic, of which we consider the tasting and smelling of the drug during its administration of great importance. This is particularly necessary in those cases in which there is a history of previous conditions that would point to already damaged liver cells. When jaundice develops, the patient should be taken off all arsenical treatment, should be given rest in bed, free catharsis, and milk diet and should immediately receive 3 c.c. intramine intramuscularly. Three days later this injection should be repeated and one week later 5 c.c. should be given. In the early combined jaundice when the icterus has disappeared, the patient should receive no further antisyphilitic treatment for one month. He should then be carried on carefully on mercury and potassium iodide with proper intervals of rest. No further arsenical treatment should be given for at least one year. In late combined cases the patient, when the icterus has disappeared, should have no further antisyphilitic treatment for one month. He may then be given a three months' course of mercury and potassium iodide. Following this he should have a month without any antisyphilitic treatment. At the end of the month's rest he may receive one small dose of an arsenical preparation followed a week later by a full dose, and he should receive eight weeks' mercury and potassium iodide. This should be followed by one month's rest and the course then repeated as often as indicated. At the first sign of intolerance to arsenic intramine should be administered. In both this and the preceding types during the month's rest from antisyphilitic treatment following the subsidence of the icterus the patient should receive general tonics.

In conclusion we take great pleasure in acknowledging the encouragement given and the assistance rendered to us by Colonel W. T. M. MacKinnon, Officer Commanding this Hospital, by Colonel C. Martin, of the Staff of Consultants, and the assistance rendered to us by the staff of the laboratory and by Lieutenant Mignault of the Syphilis Service of this Hospital.

CONCLUSIONS

1. Jaundice occurring during early syphilis is of two types:

(a) Syphilitic, in which the jaundice may appear before treatment or may be provoked by the Herxheimer reaction, appearing within the first three weeks after the first injection of the arsenical preparation. Pathologically this condition is a diffuse degeneration of the liver cells produced by the toxic action of the Treponema pallidum.

(b) Combined syphilitic and arsenical, appearing after the fourth injection of the drug. The pathology of this condition is the same as that of the preceding group. The causative factor is primarily a syphilitic degeneration of the cells on which is superimposed the toxic action of the arsenic.

2. Jaundice due to the combined action of syphilis and arsenic is not an obstructive jaundice, but is characterized by a diffuse degeneration of the liver cells.

3. Every case of syphilis, whatever the stage, should be carefully examined for any previous or present condition that would produce a damaged liver and such cases treated with the greatest of care in order to prevent the occurrence of jaundice.

4. Every case of syphilis under treatment should be carefully observed for any reaction following each injection of the arsenical compound. We consider the taste or the smell of the drug during or after the injection an important sign of early intolerance. Should any reaction occur or any sign of intolerance develop, the patient should immediately be placed on a course of intramine.

5. Intramine is apparently a specific for early or late combined syphilitic and arsenical jaundice. It is also apparently a specific to prevent the arsenical compounds from exerting a toxic action, particularly on the liver.

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FOUR FATALITIES FOLLOWING SALVARSAN*

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OUR knowledge concerning the toxicity of salvarsan and related preparations is incomplete, though certain definite reactions are recognized as occasionally following its administration with frequently alarming and sometimes fatal consequences. Difficulty is at once encountered in attempting to classify these reactions. With the exception of the small group that presents itself as a hemorrhagic encephalitis no very clear line of demarkation exists between these various types of reaction. However, the following reactions have been described:

1. *Anaphylactoid reactions,* appearing during the administration of the drug, lasting 15 to 30 minutes and characterized by sensations of burning in the mouth, flushing of the face, injection of the mucous membranes, facial edema, nausea, vomiting and a sense of suffocation. Occasionally the pulse becomes weak, pallor and finally unconsciousness intervenes. Very rarely the patient dies. The anaphylactic nature of this reaction has been investigated by Swift in guinea pig experiments.[1] He believes that by salvarsan injections the patient's own serum may be sensitized—so changed that it acts like a foreign protein and is chiefly responsible for the reaction.

2. *Deferred reactions,* appearing several hours after the administration of the drug, lasting 12 to 24 hours and characterized by chills, headaches, vertigo, nausea, vomiting, diarrhea, fever, generalized pains and occasionally skin eruptions.

3. *Late reactions,* appearing after 24 hours, and often not until the second or third day. Probably the majority of the fatal cases fall into this group. Beginning mildly with vomiting, diarrhea and fever these cases rapidly manifest headache, muscle twitching, dilated pupils, absent reflexes and after a brief illness die in coma.

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[1] Jour. Am. Med. Assn., 1912, lix, 1236.

4. Other untoward effects, though less alarming are encountered in, (a) *Herxheimer's reaction,* in which there is an intensifying of the leutic rash, said to be due to the sudden liberation of endotoxins, or to insufficient dosage; (b) the so-called *neurorecurrences,* in which neuritis develops in the cranial nerves, but especially in the optic and auditory nerves, an effect probably produced by the stirring up of a preexistent process in these locations; (c) morbilliform skin eruptions; (d) jaundice; (e) albuminuria.

EXPLANATION OF REACTIONS

The literature on this subject is crowded with explanations for these striking, often dramatic phenomena. Among the commonest encountered are: disregard for the usual contraindications (cardiovascular diseases, nephritis, advanced tertiary syphilis, etc.), employment as a last resort in the critically ill, idiosyncrasy, overdosage, failure to use sterile, distilled water, solutioin used too hot or too cold, volume of solution too great or too little, solution too acid, administered too rapidly, food or exercise before or after administration. Shamberg, Kolmer and Raiziss[2] have pointed out that the most important factor is probably the drug itself.

Ehrlich showed that the drug exposed to the air either in the dry form or in solution for any considerable length of time acquired toxic properties through oxidation and the formation of arsenoxide. Arsphenamine is not a pure chemical substance and no two batches are therefore exactly alike, each varying in its toxic and therapeutic properties. As Shamberg and his coworkers have shown, unfavorable reactions from arsphenamine are probably the result of impurities in the drug—unidentified by-products of synthesis, which for want of precise definition are spoken of as *substance X.* In their opinion the presence of this substance in certain batches of arsphenamine is undoubtedly the cause of the toxic phenomena encountered.

The four cases here reported fall into the third group of reactions. All followed an intensive course of salvarsan treatment consisting of four to six intravenous doses. There was an average interval of four days between injections. Four to six tenths grams of salvarsan were given at a time. Two days in three cases, and three days in the other case intervened between the time of the last salvarsan treatment and the onset of the illness. The time elapsing between the admission to the hospital and death was two days in three cases and one day in the other. A striking similarity in symptoms, as well as in post-mortem findings existed in all four cases. After a symptomless latent period of about two days the development of sudden and profound coma was characteristic and dominated the clinical picture so that it was difficult to elicit any focalizing signs at all. There were no cranial nerve palsies. The pupils were dilated in two cases, in two unaffected. During the last twenty-four hours of life the reflexes disappeared in all four cases. Half of the cases had convulsions. Cheyne-Stokes breathing was present in all cases and death was apparently due to failure of the respiratory center.

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[2] Jour. Cutan. Dis., May, June, 1917.

Pathologic study of the brains of these four cases showed similar lesions. These consisted in minute hemorrhages, scattered through and confined to the basal nuclei and that part of the cerebrum bounding the lateral ventricles. These were associated with a softening confined to this locality and seen easiest on gross examination. Cerebral congestion and edema were marked. Increase of cerebrospinal fluid was not a conspicuous finding. In only one case was there a slight fatty degeneration of the liver.

These fatalities all occurred in healthy young men. Four cases occurring at one time could hardly be explained as an idiosyncrasy. The technic of administration can be exonerated in view of the fact that hundreds of other injections were given by the same method without reaction. The cause of these mishaps is undoubtedly to be found in the toxic by-products of salvarsan synthesis, the exact nature of which is unknown.

CASE I.—C. F. 24 yrs. white male.

Family and Personal History.—Father died of T. B. Mother died of cancer. One sister died of diphtheria. One sister living and well. Paymaster. Moderate in use of alcohol.

Past History.—Two attacks of gonorrhea. Proctitis Dec. 1917. Secondary lues March, 1918, manifested by mucous patches, macular eruption and general adenitis. Wassermann ++++. Salvarsan Feb. 28, .4 gm., Mar. 4, .6 gm., Mar. 8, .6 gm., Mar. 11, .6 gm., Mar. 15, .6 gm., Mar. 18, .6 gm. No immediate reactions.

Present Illness.—On admission to Hospital Mar. 20 history unobtainable on account of semicomatose condition and convulsions. Patient is well developed and well nourished. Heart, lungs, abdomen and genitourinary system normal. General adenitis. Mar. 21 A.M. Patient more stuporous, sweating profusely.

Eyes directed upward and to the right. Slight exophthalmus, more on left. Head drawn strongly to right. Change of direction is disturbing. Lines of mouth and face flat on left side. Pupils equal, regular and react promptly to light. Incontinence of urine and feces. Breathing at times slow and shallow. Pulse slow, irregular, and of poor quality. Knee jerks equal, but diminished. Clonus absent. Babinski's sign positive on both sides. Kernig negative. No rigidity of neck. 2nd day: eye grounds normal, no choked discs. Cheyne-Stokes breathing. Flaccid paralysis of both arms and legs. Abdominal and cremasteric reflexes absent. Babinski's sign present. 8 P.M. Tonic spasms lasting 10 to 20 seconds. Tongue deviated to right. Mar. 22nd Diagnosis: cerebral hemorrhage. Temporoparietal decompression done without positive findings. 6 P. M. died.

Urine: Acid; faint trace of alb.; no casts. Spinal Fluid: Globulin +++, no increase of cells. Culture sterile.

AUTOPSY, MARCH 23, 1918, 20 HOURS POSTMORTEM

External Examination.—Body that of a young man, well developed and well nourished. 180 cm. in length. Moderate rigor mortis. Hypostatic congestion of the back. No enlargement of superficial lymph glands. No jaundice. Skin smooth. No deformities. There is a sutured surgical incision over the right parietal region, semilunar in form and 18 cm. in length. Surrounding tissues show a moderate degree of edema and congestion. The exposed calvarium shows a trephine through the right parietal bone 5 cm. × 3 cm. Pupils contracted, equal and regular. Conjunctivæ clean. Ears and nose normal. Mucous membrane of mouth pale and covered with a few streaks of blood. Several gold teeth. Remaining teeth in good condition. Genitalia normal.

Internal Examination.—Brain. A clot plugs the trephined opening through the parietal bone. This adheres to the edges of the bone on removing calvarium. Under this there is a small incision through the pia, 1 cm. in length. Over the whole surface of the right hemisphere, the pia and dura are dry and free from blood except for the area corresponding to the trephined opening. On the contrary, over the whole surface of the left hemisphere there is a thin layer of recent blood. There are no clots and the blood is apparently from a few ruptured small veins in the neighborhood of the falx cerebri. There is marked congestion of all the superficial veins. There are no alterations in any of the cerebral arteries. The meninges are normal. There is no increase of cerebrospinal fluid. On section throughout both lateral ventricles there is a thick sprinkling of subependymal hemorrhages. The ependymal lining itself is dull and roughened. There is no exudate, however, and no evident increase of interventricular fluid. The third and fourth ventricles show no such alteration. For a distance of 3 to 4 cm., extending into the substance of the brain about the lateral ventricles on all sides there is a marked change. This consists in an extreme softening of the brain tissue with many punctate hemorrhages scattered throughout. The following structures are involved in this process: the splenium of the corpus callosum, the fornix, the caudatum, internal capsule, the optic thalamus, hippocampus, cruri cerebelli and parts of the temporal and occipital lobes. Without softening the same small hemorrhages can be demonstrated on section of the parietal lobes in limited areas. The midbrain, pons, medulla and upper cord are normal.

Chest: Lungs: Pleural surfaces smooth and shiny. Air containing throughout. On section pinkish red in color. Small amount of blood-tinged frothy fluid can be expressed from both lungs. Bronchi normal. Heart: normal in size and position. Epicardium, myocardium and endocardium show no change. Valve leaflets normal. Foramen ovale closed, coronaries normal. Ostia measure in circumference: aortic valve, 6 cm.; pulmonic valve, 6 cm.; mitral valve, 9 cm.; tricuspid valve, 12 cm.

Abdomen: Peritoneum shows no fluid, smooth throughout. All organs normally disposed. Appendix retrocecal in position. Spleen: Small.. Surface smooth. On section, pinkish violet background on which the gray lymph follicles stand out prominently. Vessels and trabeculæ normal. Liver: small. Surface shiny. On section, pale yellow in color. Firm. Central veins stand out prominently. Gall bladder and ducts normal. Kidney: Normal in size and consistence. Capsule strips easily. On section there is no change demonstrable over the normal. Vessels, pelvis, ureters normal. Pancreas and adrenals normal. Bladder: Distended with clear amber urine, mucous membrane normal. Stomach: Contains dark brown material. Marked autolytic change in the stomach mucosa.

Internal and middle ears normal.

Microscopic Examination.—Brain: Scattered through all sections taken from the areas showing gross changes, numerous patches of recently extravasated erythrocytes stand out prominently. The largest of these areas measures about 1 mm. in diameter. The cortex appears to be free from these changes. Engorgement of the vessels is a prominent feature of all sections, and there is a moderate amount of edema to be made out. Ganglion cells show no alteration. Neuroglia also appears normal. No wandering cells. No thrombi.

Liver: Slight increase in connective tissue about central veins. Some atrophy of liver cells with pigmentation. Outside of these areas the liver cells appear unchanged.

Lung: Many alveoli filled with a pink staining material in which large pigmented epithelial cells predominate. A few alveoli adjacent to bronchioles contain polymorphonuclear leucocytes in addition.

Kidneys: Moderately congested vessels. No other change.

Heart: Normal.

Spleen: Normal.

Adrenals: Unchanged.

Anatomic Diagnosis.—

1. Encephalitis, acute, hemorrhagic.
2. Ependymitis, acute, hemorrhagic, (lateral ventricles).
3. Cerebral congestion, acute.
4. Operative wound and trephine, right side, near midline of skull and posterior to Rolandic fissure.
5. Fatty degeneration of the liver, slight.

CASE 2.—J. C., 25 yrs., white male.

Family and Personal History.—Father died at 48 of pulmonary T. B. Otherwise negative. Sore on penis summer 1916. Photographer. Moderate use of alcohol.

Past History.—Secondary lues. Wassermann ++. Salvarsan March 8, .4 gm.; March 11, .6 gm.; March 18, .6 gm.; March 22, .4 gm.; March 26, .4 gm. No immediate reactions.

Present Illness.—Found by doctor 11 A. M., March 28, comatose. Transferred to hospital with diagnosis of epilepsy. On admission well developed young man, unconscious, normal reflexes. Pupils react well to light, equal. Lies quietly in bed, occasionally moving legs and arms. Unable to swallow. Heart, lungs and abdomen normal; 3 P. M., unconscious, knee jerks and Achilles jerks present. Abdominal and cremasteric reflexes diminished. No twitching of muscles. Moves arms and legs. Apparently growing weaker. March 29, A.M., spent a quiet night. No evidence of paralysis. No convulsions. Cheyne-Stokes breathing. Unable to swallow. Pulse irregular. Pupils slightly dilated. P. 110; T., 104°; R., 30. Died at 1 P. M.

Urine: cloudy; faint trace of alb. Many granular casts; few W. B. C. and R. B. C.

AUTOPSY MARCH 30, 1918. 24 HOURS POSTMORTEM

External Examination.—Body that of a young man, well muscled and showing no emaciation, 157 cm. in length. Rigor mortis present. Hypostatic congestion of back. No rash, edema or jaundice. No enlargement of cervical, axillary or inguinal glands made out on palpation. Ears and nose normal. Pupils equal, regular and in mid-dilation. Mouth and teeth show no change. Genitalia normal. Hair distribution male type. No deformities.

Internal Examination.—Brain: Dura mater shows no change except for marked congestion of all its vessels. No increase of cerebrospinal fluid. Convolutions of whole surface greatly flattened. Vessels show no alteration. On section the ependyma of the anterior half of the lateral ventricles is dull and opaque and the site of many small hemorrhages. There is no change in the posterior horns, or in the third or fourth ventricles. Serial section from before back shows areas of extreme softening of the brain tissue with marked hemorrhages into these areas. This softening is sharply localized to the floor of the lateral ventricles, and involves the caudatum on both sides, both internal capsules, the lenticular nucleus and the optic thalamus bilaterally. The internal capsule is the scene of the most extensive destruction. The remaining cerebrum and cerebellum show no gross changes. The midbrain, pons and medulla are unaltered.

Cord: Membranes normal. Moderate congestion of superficial vessels. There are no changes to be made out on many cross-sections of the cord at different levels. Middle ears: normal.

Chest: Left chest contains about 150 c.c. of blood-tinged, clear fluid. The right chest about 50 c.c. of the same kind of fluid. Pleural surfaces smooth. Heart in normal position. Lungs: Right lung. Slightly more voluminous than normal. Upper lobe posteriorly and at apex adherent. Dark red in color. On section much bloody froth flows from the tissues. Bronchi normal. Few enlarged bronchial lymph glands. Left lung presents the same appearance. Heart: Normal size. Pericardium normal. No excess of fluid in sac. Moderate increase of epicardial fat. Myocardium and endocardium show no changes. Foramen ovale closed. Coronaries normal. Ostia measure in circumference: aortic valve, 7 cm.; mitral valve, 9 cm.; tricuspid valve, 12 cm.; pulmonic valve, 8 cm. Aorta: Smooth and elastic throughout. Diaphragm extends to the 4th rib on right and to the 5th rib on the left.

Abdomen: Organs normally disposed. Appendix free and hangs over pelvic brim. Peritoneum everywhere smooth and shiny. Liver: Normal in size. Slightly softer than normal. Surface smooth and reddish brown with matted yellowish areas. On section same reddish brown color evident with a similar mottling. Lobules regular and of normal size. Surface smooth. Moderately soft. On section the lymphoid follicles are more prominent than normal. Vessels and trabeculæ show no change. Kidneys: Normal size. Surface smooth after stripping capsule. No alteration seen on section in medulla, cortex or pelvis. Ureters normal. Adrenals, pancreas and testicles normal. Bladder: 600 c.c. clear amber urine. Mucous membrane normal. Stomach and intestines show no alterations.

Tongue: Marked hyperplasia of lymphoid tissue at base.

Tonsils: Cyst of the left. Both cryptic and fibrotic.

Thyroid: Each lobe measures 4 × 3 ×1 cm. No alteration made out on section.

Thymus: 18 cm. in length. Rather markedly larger than usual. Pinkish, firm gland tissue remaining.

A chain of pea-sized lymph glands can be traced down the neck to the arch of the aorta.

Microscopic Examination.—Brain: Small focal hemorrhages. No destruction of erythrocytes. No pigment. No wandering cells to be found. In the subependymal region the nuclei of the neuroglia cells stain poorly and are pyknotic. The nerve fibers also take the stain badly. The ganglion cells show no alteration. All of the vessels are moderately congested. No thrombi.

Cord: No demonstrable changes.

Lungs: Heavy deposits of pigment about bronchi. All the alveoli are filled with light pink hyaline material, in which a few desquamated cells have been caught. Marked congestion of all the capillaries.

Bronchial glands: Heavily pigmented. Marked congestion.

Spleen: The pulp is stuffed with a great many erythrocytes. The splenic cells are unchanged. Malpighian corpuscles are normal in size and appearance.

Liver: No noteworthy changes.

Kidney: Slight degree of cloudy swelling of the epithelium the only change evident.

Heart: Normal.

Anatomic Diagnosis.—1. Encephalitis, acute, hemorrhagic—involving the caudate nucleus, both sides, internal capsules, lenticular nuclei, optic thalami.

2. Ependymitis, acute, hemorrhagic, lateral ventricles.

3. Cerebral congestion and edema, acute.

4. Pulmonary congestion and edema, acute.

5. Hydrothorax, bilateral (postmortem).

6. Hyperplasia of the lymphoid follicles of the spleen and at the base of the tongue.
7. Persistent thymus.
8. Enlarged cervical glands.
9. Fibrosis of the tonsils, bilateral.
10. Cyst of the left tonsil.
11. Pleurisy, chronic adhesive, right upper lobe, posteriorly.

Arsenic demonstrated in the urine.

CASE 3.—D. S., 29 years., white male.

Family and Personal History.—Father died at 82 of epithelioma of lip. One brother died at 24 of rheumatism. Plasterer. Moderate use of alcohol. Gonorrhea in 1916. Discharge stopped 4 weeks. Noticed sore on penis April, 1917, disappeared after 2 weeks.

Past History.—Secondary lues. Wassermann ++++. Salvarsan intravenously March 15, .5 gm.; March 18, .6 gm.; March 23, .4 gm.; March 26, .6 gm. No immediate reactions observed.

Present Illness.—Comatose when first seen by a doctor, 12 A. M., March 29. Immediately sent to hospital. On admission patient appeared unconscious, hypersensitive, pupils dilated, reacting well to light, reflexes exaggerated, no paralysis. Remaining physical examination failed to disclose anything worthy of note. Quiet, unable to swallow, pulse regular. March 30, A. M., unable to swallow. All muscles relaxed. Left pupil dilated. Conjunctiva right eye injected, patient very weak. Slight external strabismus. Head retracted and rigid. Cheyne-Stokes respiration in cycles of half a minute. Pulse regular, 44. Lungs normal. Abdominal reflexes absent. Left cremasteric reflex absent. Slight bilateral Kernig. No clonus. Both legs and arms flaccid paralysis. Both knee jerks absent. No Schaffer, Gordon or Babinski signs. Oppenheim's sign slight. Chaddock's sign present on right. T., 101°; P., 60; patient growing gradually weaker. Urine: acid; faint trace of alb. No casts. Many R. B. C. Blood: R. B. C., 5,200,000; W. B. C., 9,800; S. L., 13; L. L., 5; E., 3; N., 78; B. I. Culture sterile.

AUTOPSY MARCH 30, 1918. 5 HOURS POSTMORTEM

External Examination.—Body that of a young male adult about 30 years of age, well nourished and well developed, measuring 167 cm. in length. Skin is smooth and there is no edema, jaundice or eruption. Hair scant on head, elsewhere normal. Rigor mortis undeveloped. Livor mortis of back. Axillary, inguinal and cervical glands not enlarged. No deformities. Ears and nose clean. Pupils slightly irregular and in mid-dilation, left a little larger than the right. Few carious teeth. Genitalia normal.

Internal Examination.—Brain: Dura mater normal. Moderate increase of clear fluid in subdural space. Congestion of all superficial vessels on surface of brain. Marked flattening of the convolutions. No alterations of any of the cerebral arteries made out. On section the ependyma lining the lateral ventricles is dull and peppered with small pinpoint hemorrhages. This is particularly marked in both posterior cornua and the under surface of the fornix and corpus callosum. There is a slight increase of intraventricular fluid, which is clear. No such change is to be noted in the third and fourth ventricles. Extending for a distance of 1-2 cm. into the substance of the brain about the lateral ventricles from the posterior border of the optic thalamus to the level of the stria acusticæ in the medulla there is a marked softening with a moderate sprinkling of small hemorrhages. This area of softening and hemorrhage involves the posterior half of the fornix, the splenium of the corpus callosum, midbrain, pons, upper half of the medulla, and the parts of the occipital lobes. No gross lesions other than those described can be demonstrated anywhere in the cerebrum or cerebellum.

Cord: Membranes normal. Slight engorgement of surface vessels. No gross changes can be shown on several sections.

Chest: Vault of the diaphragm extends to the 4th rib on right, 5th rib on left. Right chest cavity dry, pleura smooth and shiny. Left chest contains about 200 c.c. of brown fluid. Left pleura and parietal pericardium stained brown. Dirty, ragged opening into esophagus from left pleural cavity just above cardiac end of stomach. Heart in normal position. Lungs: Right lung normal in size. Surface smooth. Lung moderately air containing. On section, dark-red in color, and drips a frothy, red fluid. Bronchi normal. Left lung differs in no way from right. Bronchial lymph glands not enlarged. Heart: Normal in size. Pericardium shows no change. No increase of fluid in sac. Myocardium firm and deep red. No scarring. Endocardium shows no alteration. Cusps normal. Circumferential measurements of the ostia: aortic valve, 6.5 cm.; mitral valve, 10 cm.; pulmonic valve, 7 cm.; tricuspid valve, 15 cm. Length of left valve, 8 cm. Thickness of left valve, 1.5 cm., right valve, 2-3 mm. Coronaries normal. Foramen ovale closed. Aorta: Many fine furrows showing through the intima throughout its whole length. Several puckered, flat atheromatous scars, the largest measuring 1.5 cm. in diameter and lying at the beginning of the descending aorta. No marked loss of elasticity.

Abdomen: Organs normally disposed. Appendix free and normal. Peritoneum smooth and normal, except that covering the bladder which is very dark red in color. Spleen: Enlarged, 13 × 8 × 4 cm. Surface smooth. Moderately soft. On section the lymphoid follicles are very prominent against the soft, dark-red background. Liver: Normal size. Surface smooth. Normal consistence. On section, reddish-brown. Lobules normal. Gall-bladder normal. Ducts patent. Kidneys: 12 × 6 × 5 cm. Firm. Capsule strips easily, leaving smooth, dark-red surface. On section cortex bulges slightly. Dark red in color. No other change in cortex or medulla except at the lower pole of the left kidney there is a cyst 2.5 cm. in diameter. It contains a dark-brown fluid. Ureters, pelvis, vessels normal. Adrenals normal. Bladder distended with 500 c.c. of slightly reddish, amber urine. Mucous membrane dull in color. There are many widespread submucous hemorrhages. Prostate and seminal vesicles normal. Testicles normal. Pancreas, stomach and intestines normal. Tonsils normal. Tongue: Marked lymphoid hyperplasia at base. Thyroid, 5.2 × 2.5 × 1.5 cm. Measurement of each lobe. No change noted on section. Thymus. Replaced by fat for most part.

Microscopic Examination.—Brain: Congestion of capillaries. Many scattered small hemorrhages, recently extravasated erythrocytes. About some of the vessels there is an amorphous pink staining material, evidently edema. No other changes noted. Ganglion cells unaltered. Cord appears normal throughout. No thrombi.

Lung: Moderate congestion of capillaries. No edema.

Heart: No alteration.

Kidney: Rather marked congestion of all vessels. No other changes made out.

Liver: Hepatic cells about central veins rather widely separated. Otherwise there is nothing noteworthy.

Thyroid, pancreas and testicles normal.

Thymus: A great part of the original thymic architecture is preserved. No changes are to be made out in either small or large thymic cells nor in Hassall's corpuscles.

Tonsil: Small, subepithelial abscess.

Adrenal: Congested.

Anatomic Diagnosis.—1. Encephalitis, acute, hemorrhagic (involving posterior half of fornix, splenium, midbrain, pons, upper half of medulla, and parts of both occipital lobes adjacent to posterior horns of lateral ventricles).

2. Ependymitis, acute, hemorrhagic (lateral ventricles).
3. Cerebral congestion and edema, acute.
4. Pulmonary congestion and edema, acute.
5. Congestion of viscera, acute.
6. Cystitis, acute, hemorrhagic.
7. Aortitis, chronic (syphilitic).
8. Hyperplasia of lymphoid tissue of spleen and at base of tongue.
9. Cyst of left kidney.
10. Cyst of left choroid plexus.
11. Rupture of esophagus into left thoracic cavity (postmortem).

Case 4.—E. H., 28 years, white male.

Family and Personal History.—Mechanic. Moderate use of alcohol. Denies venereal disease. Previous personal history unimportant. Family history negative.

Past History.—Secondary lues. Wassermann ++++. Salvarsan intravenously, March 11, .5 gm.; March 15, .6 gm.; March 18, .6 gm.; March 22, .4 gm.; March 26, .6 gm. No immediate reactions following any of these injections.

Present Illness.—March 29 complained of a cold. Went to the doctor again the same day with the same complaint. Found delirious same night and admitted to hospital. Condition on admission as follows: unconscious, restless, irritable, unruly, making purposeless motions. Pupils dilated, equal, regular. Hypersensitive, vomited greenish material. No rigidity of neck. No Kernig. Knee and Achilles jerks normal. Abdominal and cremasteric reflexes present. Remaining physical examination revealed no further abnormality. March 30, 9 A. M.: Less restless. Neck retracted. Pupils dilated, left more than right, but both react readily to light. Resists examination of eyes. Systolic murmur over pericardium most marked at apex. Otherwise heart and lungs normal. Cremasteric and abdominal reflexes absent. Patient too violent to elicit Babinski's sign. Gordon on left. Chaddock on right. Knee jerks diminished, but equal. Unconscious. T., 102.4°, rectal; P., 72; Res., 20. 1 P.M.: Head drawn back. Jaws tightly closed. Bites tongue. Clonic convulsions over entire body, lasting about 3 minutes. Frothing at the mouth. In interim is groaning as if in pain. Restless. Pulse, good. 3 P.M.: Twitching of muscles of face and arms. Profuse perspiration, coughing at intervals, facial grimaces, appears to be in pain. 7 P. M.: Short convulsive attacks have continued. Skin warm and moist. Corneal reflex absent, eyes rolling to left, pupils dilated. Stertorous breathing, quieter. P. 110; R., 35. Gradually growing weaker. Vertical nystagmus left eye. Fundus normal.

Died 2:15 A. M., March 31.

Urine: Acid; cloudy; faint trace of alb. No casts.

Blood: R. B. C., 5,130,000; W. B. C., 12,000; Hgb., 90; S. L., 7; L. L., 3; T. I; N. 89.

Spinal fluid 20 c.c. under normal pressure, clear, no globulin, no increase of cells.

AUTOPSY MARCH 31, 1919. 11 HOURS POSTMORTEM

External Examination.—Body is that of a muscular, well-nourished young male adult, 171 cm. in length. Rigor mortis present. Livor mortis of back. No enlargement of cervical or inguinal glands. No eruptions. No edema. Ears and nose clean. Right pupil in mid-dilation and regular. Left larger, but regular. Teeth clean. Mucous membrane of mouth normal. Genitalia normal. No scar on penis. Few shotty glands in both axillæ.

Internal Examination.—Brain: Vessels of dura mater markedly congested. No other change in dura. Cerebral vessels also greatly distended with blood. Convolutions greatly flattened. No increase of cerebrospinal fluid. Cerebral arteries normal. Section of the brain shows a striking change in and about the lateral ventricles. The whole ependymal lining is extremely red, swollen and dull in color. This is not true in the third or fourth ventricles. Serial section of the brain from before back shows intense engorgement of all the vessels. The pins and the left crus-cerebri are the scene of a thick scattering of small hemorrhages. There is a distinct softening accompanied by small hemorrhages in the fornix and corpus callosum. No other changes are to be made out in any other part of the brain. Cord: Membranes normal. No alteration is to be seen either on the surface or on section at any of the different levels. Internal and middle ears normal. No thrombi.

Chest: Vault of diaphragm extends to the 4th rib on right and to 6th rib on the left. Heart and lungs in normal position. Heart: Normal in size. Pericardium normal. No increase in pericardial fluid. Muscle uniformly dark red. No scars. Endocardium smooth throughout. Valve leaflets smooth and approximate well. Coronaries normal. Foramen ovale closed. The ostia measure in circumference: aortic valve, 7.5 cm.; pulmonic valve, 8 cm.; mitral valve, 10 cm.; tricuspid valve, 12 cm. Length of left ventricle, 8 cm. Thickness of wall of left ventricle, 1.5 cm.; thickness of right ventricle wall, 2-3 mm. Lungs: Both lungs voluminous. Surface smooth and dark red in color. On section a great amount of blood-tinged froth pours from the lung substance. The cut surface is red in color. There is no other change. Bronchi normal.

Abdomen: Organs normally disposed. Peritoneum, smooth and shiny. Appendix, free and normal. Liver: 26 × 23 × 7 cm. Weight about 2300 gm. Surface smooth and dark red. Moderately firm. On section dark red in color. No alteration in lobules. Knife scraped across the cut surface brings away a quantity of bloody fluid from the tissues. Gall-bladder and ducts normal. Spleen: 18 × 11 × 5 cm. Weighs about 500 gm. Capsule, dull, thickened and puckered on diaphragmatic surface. Reddish purple in color. Section: Fairly firm, dark red background. Lymphoid structures moderately prominent. Trabeculæ, normal. Kidneys: 12.5 × 6.5 × 3.5 cm. Capsule strips readily, leaving a smooth, dark red surface. On section cortex and medulla, normal thickness, dark red in color. The pelvis and ureters appear normal. Adrenal normal. Stomach and intestines normal. Bladder contains about 300 c.c. clear amber urine.

Thyroid: 5.5 × 3.5 × 2.5 cm. Normal. Thymus replaced by fat. Pancreas and testicles normal.

Tongue: Marked hyperplasia of lymphoid follicles at base of tongue. Tonsils cryptic.

Aorta: Longitudinal wrinkling and yellow streaks seen from within, particularly marked near arch, but occurring throughout whole course.

Microscopic Examination.—Heart:—Fragmentation of muscle fibers.

Lungs: Alveoli filled with pink staining material, desquamated cells and a few polymorphonuclear leucocytes. Moderate congestion of vessels.

Liver: No noteworthy changes.

Kidney: All the capillaries including those of the glomerular loops are loaded with red blood cells. On this account the glomeruli appear larger than normal. There are no other demonstrable changes.

Spleen: There is a marked congestion of the pulp and larger vessels with well preserved erythrocytes. The follicles stand out prominently, the small lymphocytes crowding in upon the germinal centers.

Lymph gland: Hyperplasia of lymphoid elements with extensive polymorphonuclear infiltration.

Tonsils: Hyperplasia of lymphoid tissue.

Brain: Small scattered hemorrhages averaging about 1 mm. in diameter. Erythrocytes well preserved. No polymorphonuclear leucocytes. No wandering cells. All capillaries greatly engorged. No necrosis, but there are wide clear spaces in the tissues probably due to edema. Ganglion cells are not altered. No thrombi made out.

Cord: No alterations.

Anatomic Diagnosis.—1. Encephalitis, acute, hemorrhagic, involving corpus callosum, fornix, left crus, cerebelli and pons.

2. Ependymitis, acute, hemorrhagic (lateral ventricles).

3. Cerebral congestion and edema, acute.

4. Pulmonary congestion and edema, acute.
5. General congestion of all viscera, acute.
6. Enlargement of the spleen.
7. Hyperplasia of the lymphoid tissue, base of tongue.
8. Aortitis, chronic, (syphilitic).
9. Perisplenitis, chronic, localized.

Arsenic found in urine.

THE INTENSIVE TREATMENT OF WOMEN WITH NEODIARSENOL*

Procedure and Result at the Hospital Jail of San Juan, Porto Rico

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(Received for publication, July 28, 1919)

IN a former paper, "The Intensive Treatment of Women with Arsenobenzol (Schamberg)," I gave a brief outline of the rationale and method used in treating fifteen women with active syphilis and seven in the latent tertiary stage with four-plus positive Wassermann reactions. At that time, I mentioned that the results of using neodiarsenol in a similar manner would be the basis of another communication. (Cf. Am. Jour. Syph., iii, No. 3, p. 449.)

In our work at the Hospital Jail of San Juan, P. R., it was our purpose to treat the patients so as to keep them noninfectious even after leaving the institution, since it was realized that it would not be possible to keep them from practicing their profession on their release. Fifty-two patients with three- or four-plus positive Wassermann reactions, although free of active syphilitic lesions, were given the "intensive" treatment using neodiarsenol.

The method of preparation of the neodiarsenol has been described, [Goodman: Experiences with Neodiarsenol (Canadian Neoasphenamine), Med. Rec., New York, April, 1919, xcv, No. 16,] and can be dismissed here with a few words. The apparatus was sterilized by boiling in distilled water. The water for the solution was freshly distilled, and never more than four hours old. It was boiled and cooled to room temperature. The solution when made was injected immediately by the gravity method. The amount of fluid was 30 c.c. for each injection.

The first dose of neodiarsenol was 45 centigrams; the second was 60; and the third was 75 centigrams; a total of 180 centigrams injected in 48 hours.

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*Authority to publish granted by the Surgeon-General's Office, Washington, D. C.

The patients were given a cathartic the night preceding the first injection, and were on a limited fluid diet for the three days.

Except in one patient who was pregnant, and complained of abdominal pains, there was no general reaction. This patient received only two injections, one of 45 cg. and the second of 75 cg. In two cases mechanical difficulty with small veins and nervous patients prevented the injection of the third dose. In two other cases, poor technic on the second day led to infiltration and the third dose was not given. Happily, the expectations that sloughing and ulcer would result were disappointed.

In nearly every case, three or four intramuscular injections of grain doses of mercury salicylate had preceded the neodiarsenol therapy.

The Wassermann was repeated in all except nine cases, fourteen days after the last injection. It has not been possible to repeat the tests since.

I shall briefly summarize the results:

Of the 43 women whose Wassermanns were reported prior to and after the series of injections:

4 reduced from +++ to negative.
15 reduced from ++++ to negative.
1 reduced from ++++ to ±
1 reduced from ++++ to +
3 reduced from ++++ to ++
    (One of whom received only two doses)
17 remained ++++
    (Two of whom received only two doses)
1 remained +++
    (She received only two doses)
1 went from +++ to ++++

If one were permitted with such small numbers to estimate percentages, they would be as follows:

Reduced to negative,	44%
Not reduced at all,	44%
Reduced slightly,	12%

In the series of seven cases of latent syphilis treated at the same time with arsenobenzol (Schamberg), six had Wassermann tests after the series of injections (See p. 664).

CASE NO.	COLOR	AGE	PRELIMINARY WASSERMANN OCT. 16	NUMBER NEODIARSENOL	NUMBER MERCURY SALICYL	SECOND WASSERMANN DEC. 6
201	Mulatto	20	Three-plus	3	3	Negative
109	White	25	Three-plus	3	3	Negative
110	White	25	Three-plus	3	3	Negative
124	Negress	20	Three-plus	3	3	Negative
134	White	22	Four-plus	3	1	Negative
200	Mulatto	19	Four-plus	3	2	Negative
137	Mulatto	18	Four-plus	3	2	Negative
155	Mulatto	19	Four-plus	3	2	Negative
132	White	20	Four-plus	3	2	Negative
300	White	29	Four-plus	3	3	Negative
203	White	15	Four-plus	3	3	Negative
199	White	20	Four-plus	3	3	Negative
127	Mulatto	18	Four-plus	3	3	Negative
123	White	18	Four-plus	3	3	Negative
34	Mulatto	20	Four-plus	3	3	Negative
107	White	19	Four-plus	3	4	Negative
65	Mulatto	21	Four-plus	3	4	Negative
29	Mulatto	25	Four-plus	3	4	Negative
23	Mulatto	22	Four-plus	3	4	Negative
214	Mulatto	18	Four-plus	3	2	Doubtful
217	Negress	25	Four-plus	2	1	Two-plus
175	Mulatto	26	Four-plus	3	2	Two-plus
128	White	20	Four-plus	3	4	Two-plus
161	Negress	32	Four-plus	2	2	Four-plus
114	Mulatto	28	Four-plus	2	3	Four-plus
162	White	19	Four-plus	3	0	Four-plus
181	Mulatto	21	Four-plus	3	1	Four-plus
213	White	37	Four-plus	3	1	Four-plus
160	Negress	30	Four-plus	3	1	Four-plus
145	White	17	Four-plus	3	1	Four-plus
210	Mulatto	20	Four-plus	3	2	Four-plus
152	White	19	Four-plus	3	2	Four-plus
143	Mulatto	16	Four-plus	3	3	Four-plus
8	Mulatto	18	Four-plus	3	4	Four-plus
4	Negress	16	Four-plus	3	4	Four-plus
12	White	19	Four-plus	3	4	Four-plus
36	Mulatto	25	Four-plus	3	4	Four-plus
42	Mulatto	18	Four-plus	3	4	Four-plus
52	Mulatto	31	Four-plus	3	3	Four-plus
70	White	22	Four-plus	3	4	Four-plus
16	Mulatto	19	Three-plus	3	3	Three-plus
74	Mulatto	18	Three-plus	2	3	Four-plus
			Cases in Which Arsenobenzol Was Injected			
61	White	34	Four-plus	3	4	Negative
37	White	25	Four-plus	3	4	Negative
54	Mulatto	30	Four-plus	3	4	Negative
60	White	18	Four-plus	3	4	Two-plus
66	Negress	25	Four-plus	3	4	Four-plus
79	Negress	35	Three-plus	3	4	Four-plus

3 reduced from ++++ to negative, or 50%
2 not reduced at all, or 33%
1 reduced slightly, or 16%

The Wassermann tests were done at the Institute of Tropical Medicine and Hygiene, San Juan, Porto Rico. We are assured from having correlated the clinical findings and the reports of this laboratory in over 2500 cases that the latter are trustworthy, and we do not hesitate to base conclusions on them.

THE TREATMENT OF LATE SYPHILIS

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(Received for publication, March 18, 1919)

FROM the standpoint of essential pathology, syphilis may be divided into three stages, first the stage before the treponemata have become generalized and before the Wassermann reaction has become positive. Even at this stage it must be recognized that the organisms can be found in the lymph nodes, spleen and possibly in the bone marrow, hence we can hardly regard the disease as strictly circumscribed, certainly not to the initial lesion. Second there is the stage of a septicemia, the old secondary stage, and third the stage of late localization in certain, often many, tissues. At times even in this stage there may be a flooding of the system with treponemata, as evidenced by the so-called recurrent secondaries.

It is now generally recognized that during the earliest of these stages energetic abortive treatment should be tried; this is the golden age to effect a permanent cure. During the second stage there is some difference of opinion as to whether or not an abortive treatment should be tried for; personally I feel strongly that it should, for there may be much to gain and nothing to lose by such a course.

Regarding the treatment of the late stages the literature is scanty, except in regard to the medication for certain special forms of late lesions, namely, those of the vascular and cerebrospinal systems. However, there are certain general points that may be emphasized, first it is extremely improbable whether any case of late syphilis has ever been cured. Warthin's observations would certainly point strongly in this direction, although certain good clinical men claim to have effected some cures. Second, any patient with an active syphilitic process must have sufficient treatment to render the lesions inactive and the blood reaction negative. Third, a small amount of treatment is dangerous, neurorecidives being especially liable to develop after one or two doses of arsphenamine. Fourth, the condition of the heart and of the large vessels must be watched just as well as the nervous system.

To take up these points more in detail, we can again repeat that there is no satisfactory evidence that late syphilis is really cured. To cause a refractory Wassermann-positive blood to become negative is indeed a triumph and a step in the right direction, but by no means a proof of cure, neither is freedom from symptoms over a space of several years, for all syphilologists realize how long a syphilitic may go without showing evident lesions. When we realize how difficult it is to cure the most favorable case it is too much to expect an old chronic to yield.

That active syphilitic processes are always a danger surely needs no further comment, but it is still a question as to just what the treatment should be. For this there are a number of reasons, all fundamental ones, dealing with the biology of the parasite, with the mode of action of arsphenamine, and with the position of the organisms in the tissues. While in experimental animals one dose of the drug will promptly kill all parasites, in man this is not true. And why is it not true? McDonagh attempts to solve the question by stating that the treponema as we know it is simply the male gamete of a parasite with a complicated life cycle, and that most phases of the cycle are not affected by the drug. His work is written largely in the language of biological chemistry and few there are who can prove or disprove it, and as yet no man has tried. Still further it has been found that the organisms gain a certain amount of resistance to arsphenamine, a resistance that is speedily lost; however, experimental work does not seem to indicate that when freely reached by the drug they should be immune to the therapeutic doses usually employed. It is usually assumed that arsphenamine actually works by killing the organisms with which it comes in contact, but some excellent men feel that *in vivo* this is not established, for instance, it is difficult to believe that the amount of arsenic in the blood serum injected into the spinal canal can be responsible for the great improvement that we frequently see in persons suffering from cerebrospinal lues. And lastly we really know but little of the time that it takes for arsphenamine bearing plasma to reach organisms that are tucked away in fibrous tissue nests; may not all of the valuable material be lost before it actually reaches the organisms? With such limitations in fundamental knowledge it is not surprising that nearly every syphilologist has a different scheme of treatment for late lesions.

There are certain men who feel that it is wise to administer a preliminary course of mercury, holding that the danger of neurorecidives is thus lessened. It would seem that if sufficient of the more potent drug be used such a procedure is unnecessary. Still others have gone to the opposite extreme, claiming that three doses in as many days will usually make the most obstinate Wassermann negative. As regarding this last point Irvine has told me that he has not found this to be the case, and his experience is considerable. Very recently Ormsby and Mitchell have stated that they consider it best to give several short courses of intensive arsphenamine therapy, with suitable elapsing intervals. Many others simply state that the blood should be rendered negative by weekly injections, employing as many as need be.

My own feeling in the matter is that it is best not to give arsphenamine at daily intervals, but at intervals of about seventy-two hours, thus there is sufficient time to guard against the dangerous late reactions. If we give four injections at such intervals, then a month of mercury injections, then another course of arsphenamine and then more mercury, we can usually accomplish the desired results. However, if within a week after the second course of arsphenamine the Wassermann still remains unchanged we should at once start in giving the arsenical at intervals not exceeding five days until a Wassermann-free blood is secured. By such a course of treatment we are not subjecting the patient to any undue dangers, the blood and serum do not have time to become arsphenamine-free for any length of time, except during the administration of mercury, and if the organisms have become arsphenamine-fast there is then time for them to lose this undesirable quality.

To recapitulate: it is generally considered unwise to give any one drug for a long space of time, inasmuch as it will lose its killing power: the old continuous method of administering mercury for year in and year out is rightly considered most unwise, and to administer arsphenamine at weekly intervals for a long space of time is probably just as bad. The general tendency is to give short and intensive alternating courses of the two drugs, with certain periods of rest if the treatment must be prolonged. Before considering a case Wassermann-fast the spinal fluid must be examined, as it is not unusual to find a focus in the nervous system in such cases.

Of course it is realized that it is absolutely impossible to lay down any hard and fast rule that will govern every particular case, for the best syphilologist is the man who can adapt himself to circumstances, but at the same time there must be some sort of a standard course from which suitable migrations can be made.

In addition to the actual treatment the kidneys must be watched, the spinal fluid should be examined if there be the least suspicion of cerebrospinal involvement, and the reflexes should be gone over at least once in two months. Also it would be a wise scheme to have an occasional eyeground examination, inasmuch as some exceptional cases will show trouble here even when the spinal fluid is but little altered. The aorta should be fluoroscoped at least once in two years.

TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

By S. T. Nicholson, Jr., Clifton Springs, N. Y.

(Received for publication, June 10, 1919)

IT HAS been demonstrated that the central nervous system is rather frequently involved in the late primary and early secondary stages of syphilis, and with this knowledge in view, a study of the spinal fluid should be made routinely. In spite of effective and easily available antiluetic treatment, and refined diagnostic methods, a large number of syphilitic patients are not thoroughly treated. This is most commonly due to failure on the patient's part to realize the importance of continuing the treatment over a sufficient period of time in view of the essential chronicity of involvement of the central nervous system; consequently it is more common than otherwise that the brain and cord become seriously involved before an attempt is made to remedy the condition, and when, owing to the advanced degeneration, the diagnosis may be made without lumbar puncture.

On account of the slowness of advanced development of tabes dorsalis and paresis in relation to the primary infection, the progress of the disease may, in tabes, and perhaps in paresis be checked, by treatment following careful spinal fluid study, for in the former particularly, there may be signs and symptoms long before the disease reaches the stage at which it actually incapacitates the patient.

Realizing, therefore, that certainly in our day these diseases will always be with us, modifications of technic which tend toward simplifying therapy, while still insuring the maximum dosage and number of treatments which can be well borne, constitute the goal to be sought. It is with this idea in mind that I am submitting this report.

The prevalence, complications, pathology, and treatment of syphilis of the brain and cord have received much consideration and have furnished material for extensive investigations which serve as a foundation for future research, and let us hope more rapid advancement in the prevention and cure of these frightful conditions.

In April, 1917, I read a paper before the New York State Medical

Society, outlining a system of treatment for intracranial and intraspinal syphilis. The essential summary of this treatment was a combination of the methods of Swift and Ellis,[1] and of Byrnes,[2] in which the patient was bled one-half to one hour after an intravenous injection of salvarsan, and the serum mercurialized by the method described by Byrnes.[2] This procedure was not dogmatically carried out in each instance, for it was not always advisable to follow an intravenous injection of salvarsan by an intraspinal injection within twenty-four hours.

As stated in this paper each worker in this field should equip himself to accurately carry out all of the well-recognized methods of intraspinal therapy and it is my conviction that the therapy should be based on the pathology in the central nervous system, the individual patient, and the stage of the disease.

It has been rather widely recognized that mercurialized serum produces a more intense reaction and irritation in tabes dorsalis than the salvarsanized serum prepared either *in vitro* or *in vivo,* and for this reason treatment has been modified in this clinic accordingly.

Owing to the time and care necessary to prepare the mercurialized-salvarsanized serum, a more simple method has been adopted, comparative results being tabulated in order to eventually determine the best method.

Since the description of the mercurialized-salvarsanized serum, which, with variations and elasticity, we consdier preferable for most patients, a few cases have been treated by draining the spinal canal immediately after intravenous injections of salvarsan, but eventually these cases were also given intraspinal treatments because we felt that their progress did not compare with that of the cases receiving intraspinal therapy, but in a clinic where the number of cases is not sufficiently great to allow one to devote one's time exclusively to such therapy, the following technic has been adopted:

A suitable donor of blood is selected, either one who has received sufficient treatment to have a negative Wassermann or a normal. Under very strict aseptic precautions 500 c.c. of blood are withdrawn from the donor into a sterile Erlenmeyer flask, the blood is allowed to clot at room temperature and then placed in the ice box overnight. The following morning the serum is pipetted off into several 50 c.c. centrifuge tubes and centrifugalized one-half hour; only the clear supernatant serum is used. For the storage of the prepared serum, small dark colored bottles (adrenalin bottles) are used. These bottles have previously been dry sterilized. Into some are put 15 c.c. of the human serum. These are then placed in a water-bath at 56° C., for one-half hour to destroy the complement and inhibitory substances in the serum. The corks are then thoroughly paraffined and the bottles placed in the ice chest. Into other bottles 1 c.c. of a solution of bichloride of mercury in redistilled, sterile water, some containing $\frac{1}{50}$ gr. and some $\frac{1}{100}$ gr. of mercury, is placed. To each bottle containing the mercury solution 12 c.c. of the centrifugalized serum are added, at first drop by drop, and well shaken after each drop is added to avoid accumulation of undissolved albuminate of mercury; the total quantity is made up to 30 c.c. by the addition of sterile normal salt solution, heated to 56° C. for one-half hour in a water bath sealed with paraffin and placed in the ice chest.

We now have the mercurialized serum complete and ready for use by warming to body temperature. We also have sterile human serum to which .5 mg. of salvarsan may be added the morning of its administration, after its addition, however, the mixture must be incubated for two hours at 37.5° C. and heated a second time to 56° C. for 20 minutes. The mercurialized serum will keep indefinitely. The sterile serum is considered safe for use so long as no sediment can be detected by agitating the bottle. I have safeguarded its use by making cultures and smears from it the day previous to its intended use. I am at present using some of this serum over sixty days old. By this method stock serum to which salvarsan in known doses can be added, and mercurialized serum ready for use can be had at hand at all times. The time and care consumed in the preparation of a number of doses is not much more than is required in the preparation of a single dose of the mercurialized-salvarsanized serum; therefore, instead of the laborious days that were previously spent in the preparation for one treatment for intraspinal injection, a few minutes is all that is necessary after the stock serum is once prepared.

The bleeding of the donor is done into an Erlenmeyer flask, dry sterilized; the needle and rubber tubing are boiled in a citrate of soda solution and a vacuum is created in the flask by using the syringe with which paracentesis outfits are equipped. No difficulty was encountered in securing hemoglobin-free serum.

Since the practice of giving intravenously smaller doses of salvarsan, and repeating them more often, has supplanted to a large extent the administration of larger doses, serum salvarsanized *in vivo* for intraspinal injections has been abandoned in this clinic and in its place, mercurialized serum, or human serum, to which a known quantity—never to exceed 0.5 mg.—of salvarsan is added, has been substituted.

DISCUSSION

The selection of the type of intraspinal therapy to meet the indications in the individual case is not difficult. In our hands the interstitial type bears mercurialized serum better than the parenchymatous type. Under the former are included such conditions as cerebrospinal syphilis which includes gumma formation, meningitis, luetica, and meningoarteritis. The parenchymatous type does better with the salvarsanized serum, although Haller[3] puts general paresis in the group that stand the mercurialized serum better than do cases of tabes dorsalis.

The treatment of my cases of paresis has been such a failure that I am almost tempted to give up trying any therapy; however, if these patients can improve for a short time, the result, even if it only renders them temporarily capable of adjusting their business affairs doubtless justifies the effort.

Owing to the established fact that the reaction following the intraspinal injection of mercurialized serum is more severe than when salvarsanized serum is used, but that the laboratory findings in the spinal fluid are more favorably influenced when the mercurialized serum is used, our patients are usually started on the salvarsanized serum, which is alternated within the next ten days with mercurialized serum in smaller doses than was formerly used, i. e., instead of using $\frac{1}{50}$ grain of bichloride of mercury as an initial dose, $\frac{1}{100}$ grain is used and gradually increased to $\frac{1}{50}$ grain which is the maximum dose used, instead of $\frac{1}{25}$ grain which was formerly used.

The remaining features of the technic aside from the preparation of human serum in stock quantities is based on previously published experimental work; for example, Swift[4] has shown that when salvarsan is added to serum *in vitro,* its spirocheticidal action is increased by heating.

As has already been noted, the plain serum is heated to 56° C., when it is first prepared and reheated and incubated when the salvarsan is added just previous to its administration.

Swift has also indicated that in his opinion salvarsan-treated patients produce a better serum than normal patients. In my method of preparation I never use the serum of patients who have had salvarsan ten days previous to the bleeding for a stock serum for obvious reasons; furthermore even the salvarsan-treated patients should in my opinion have a negative Wassermann.

There should be little necessity for a plea for intraspinal medication in syphilis of the central nervous system. Until a more effective therapy is evolved by further investigation and increased knowledge of the Treponema pallidum, we would be guilty of neglect if we failed to give our patients the benefit of the intraspinal methods of treatment at our disposal. It is recognized that in a great number of cases the use of mercury, iodides and the arsenical preparations exert a very beneficial influence on the course of syphilis of the central nervous system, especially in the incipient and early types of the disease. The tendency of syphilis of the central nervous system to relapse in spite of heroic systemic treatment is, of course, at the present time, axiomatic. Laboratory findings in the spinal fluid are often unchanged regardless of energetic systemic treatment until intraspinal therapy is begun.

CLINICAL RESULTS

Four and one-half years have now elapsed since we have had a group of cases of cerebrospinal syphilis under observation and treatment. Thirty-eight patients out of a group of approximately fifty have kept in more or less close contact with us. Interstitial cerebral syphilis including gummata and meningitis have given most encouraging results. Of the parenchymatous type, tabes dorsalis responds most satisfactorily. Comparisons between cases having had the systemic treatment alone and those having had the systemic treatment in conjunction with the intraspinal are most striking.

Included in this group of patients are four cases of general paresis, three are in institutions for the insane, one is dead. All four of these cases were given combined intraspinal and systemic treatments very early in the disease in the hope that complete mental break-down might be aborted. Treatment in these cases not only failed to benefit, but apparently ultimately may have precipitated more grave symptoms. The most deceptive feature of these cases was the fact that they were apparently in better condition just after the treatment, and this improvement may in such instances last several months. This improvement, however, in our cases proved to be only the calm before the storm.

I shall omit detailed case reports, simply stating the basis for conclusions which seem thus far justified by laboratory results, and by the clinical progress of cases as they have been reported to me in personal communications, or ascertained by re-examination. Following is an extract from a letter from a case of meningitis luetica with 7th and 8th nerve involvement; he first came under observation November 19, 1916. He had had a primary sore three months previous to admission. Six weeks previous to his entrance to the sanitarium, he began to have twitching of the left side of his face, roaring in his ears, headache and dizziness, which was rapidly followed by a facial paralysis. Wassermann reaction in his blood serum and spinal fluid was strongly positive. His spinal fluid cell count was 571 per c.mm. globulin 4 plus. He was given within two years fifteen doses of salvarsan intravenously and six doses of mercurialized-salvarsanized serum intraspinally. His blood Wassermann became negative, a slight fixation of complement was observed when .4 c.c. of spinal fluid was used. Spinal fluid cell count 8 per c.mm. He writes, "I seem to stage a remarkable 'come-back' physically. I've been apparently in good condition since shortly after I last saw you.

"At Camp Upton Base Hospital, I passed a perfect physical examination including Wassermann, etc."

This case is cited as somewhat illustrative of the results obtained in the treatment of the interstitial type of cerebrospinal syphilis, although naturally every case can not give such an unqualified "come-back" report.

Of the total number of patients treated there has been only one bed-ridden case, and that one probably not essentially so, though chiefly on account of girdle and lightning pains, he had given up walking; he was a physician, and came for treatment in 1916, after having sold his practice and automobiles. At the end of a year's treatment he resumed his practice but limited it to day work. Other reports from tabes dorsalis cases, several of whom are at the end of four and one-half years since the treatment was begun, are very gratifying. None who were treated have failed to show improvement. There is a noticeable parallel between the amount of treatment and the result obtained. A very encouraging feature is that the improvement appears to have been well sustained.

The laboratory findings have been uniformly favorably influenced and the symptoms from which relief has been experienced include pain, muscular spasm, nervousness, headaches, reduced or lost sphincter control and ataxia.

Three cases of tabes dorsalis treated by the "stock" serum, which is described in this report, have all responded well and have had no unpleasant reaction symptoms.

In conclusion, I would emphasize that as intraspinal treatments should be utilized in combination with general systemic treatments in order to attain the best results in syphilis of the central nervous system it is wise to make the intraspinal technic as simple as possible without sacrificing efficiency for simplicity. The patient as well as the disease must be considered and treated; accordingly Fraenkel's exercises, and other measures contributing to the patient's mental and physical well-being should receive proper consideration.

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Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs, Arkansas.

WM. H. DEADERICK, M.D., EDITOR

A CASE OF EXTRAGENITAL CHANCRE.—C. B. Camerer, Lieutenant Commander, United States Navy, and J. R. Poppen, Lieutenant United States Navy. United States Naval Medical Bulletin, 1919, vol. xiii, p. 551.

The interesting features of this case appear to be the following: (a) History of repeated exposure to infection on July 13, at which time he admitted having handled the genitals of the prostitute; the patient's statement to the effect that he is left-handed, and that he recalls the presence of an abrasion on his left index finger at this time. (b) The fact that he had taken careful venereal prophylaxis within eight hours following exposure. (c) The utter absence of a genital sore and, in fact, any other than the "paronychia" referred to, as appearing on the finger as stated, which doubtless was a mixed infection and the site of original inoculation. Digital chancres are by no means uncommon. The usual history corresponds to the case described. They begin as an insignificant "hangnail," a papule or ill-defined infiltration of the matrix or nail bed, and show a tendency to ulcerate and become secondarily infected with mixed pyogenic organisms. The presence of considerable purulent discharge and unusually severe pain tend to obscure the picture of a typical primary syphilide. As in the above case, the diagnosis is often not made until the appearance of secondary symptoms arouse suspicion.

CHANCRE OF THE THUMB.—L. Herman, Lieutenant, United States Naval Reserve Force. United States Naval Medical Bulletin, 1919, vol. xiii, p. 553.

M. S., ship's fitter, was referred for diagnosis to Navy Base Hospital No. 5, Brest, France, in August, 1918. He had been suffering for several weeks with a painless, indolent ulcer, situated over the terminal joint of the right thumb. This began as an insignificant scratch, which increased in size through ulceration and became rounded in outline with peripheral induration. The lesion had been treated with various cauterizing agents, but had lost none of its Hunterian characteristics. In fact, the case presented a primary lesion of syphilis with the most typical features of a true Hunterian chancre that the writer has ever seen in an extragenital lesion. There was concomitant indolent enlargement of the associated epitrochlear and anterior pectoral lymph nodes. Treponema pallidum was found in the serum expressed from the lesion. The blood Wassermann test was positive. The sore disappeared promptly after the administration of novoarsenobenzol. It is interesting to note that among approximately 1,000 cases of syphilis observed during fourteen months of foreign service, there were 4 in which primary sores appeared at sites other than the penis. Of these, one occurred in the midline of the anterior abdominal wall, just above the pubes; a second occurred on the lower lip, a third on the scrotum, and a fourth on the thumb, as just described. The patient with the chancre of the thumb offered the suggestion that the lesion might have been acquired while he was working as a plumber in the ship's lavatories. The chancre of the scrotum was interesting, in that the lesion was thought to be a hair-follicle infection, and was incised and curetted twice, and had entirely healed over before the patient, a physician, had any idea of the nature of the lesion. A few papules eventually appeared on the abdominal wall. Several of these were excised and examined for the treponema, but with negative results. The blood Wassermann test, however, was strongly positive. There is no reason to doubt that the scrotal lesion was a primary luetic sore.

GENITOURINARY SYPHILIS.—Franklin R. Wright, Minneapolis. Journal Lancet, 1919, vol. xxxix, p. 340.

Acute syphilitic nephritis is always accompanied by malignant syphilis; it is never found in the ordinary mild case. The character of the lesions that are found in the chronic cases consist of either a parenchymatous or a chronic interstitial nephritis or sometimes other lesions. Syphilitic nephritis is not accompanied by high arterial tension or a hypertrophied heart. Syphilis of the bladder is also a rare condition. It has been described as gummatous and in the small papular lesions. It occurs so rarely that we do not make a clinical diagnosis. Syphilis of the prostate is another condition which occurs as a local disease and is frequently overlooked. The testicle is the seat of late syphilis, relatively frequently compared with other genitourinary organs. We have developed in the testicles either gumma or interstitial disease. In interstitial disease the testicle becomes evenly enlarged. It is pear-shaped or egg-shaped, small end up; it is not painful; and it becomes heavy. It is slightly sensitive, but it fails to give the characteristic pain or sensation on pressure that the normal testicle does. The epididymis is attacked rarely; it occurs both in interstitial and as a gummatous inflammation.

SYPHILIS OF THE ANUS.—Chas. J. Drueck, Chicago. Mississippi Valley Medical Journal, 1919, vol. xxvi, p. 101.

Chancres at the anus occur frequently enough to be always thought of when an ulcer is seen at or about this opening. Its existence in men is almost proof positive of sodomy, but in women it may occur by accidental contact with the male organ or from vaginal discharges. The chancre may occur on the skin near the anus, between the radial folds or in the mucous membrane in the anal canal. On the free skin they resemble in appearance a chancre situated elsewhere, but when located between the radial folds or at the anal border they closely resemble an anal fissure. In the secondary stage of syphilis we find two forms of ulcerations, the mucous patch and the large ragged ulcer, a sequence of necrosis produced by the strangulation of circulation in the tissue surrounding the syphilides. In the treatment of these conditions rest and the removal of all irritating material from the intestinal tract is essential and also the interdiction of such articles of diet as might be a source of irritation later. The rectum should be frequently irrigated with some bland antiseptic such as iodoform and ichthyol emulsion in olive oil or a dry powder of iodoform, boracic acid, and the stearates insufflated. When the ulceration is considerable the author does not hesitate in making applications of silver nitrate, 30 to 60 grains to the ounce, to the ulcers, and repeating this application every two or three days, dressing the surface thereafter with one of the above-mentioned powders.

INFLUENZA AND NEUROSYPHILIS.—Karl A. Menninger, Topeka, Kansas. Archives of Internal Medicine, 1919, vol. xxiv, p. 98.

The interrelation of coincident infections is studied from the data presented by cases of neurosyphilis affected by attacks of influenza. Cases are cited to illustrate three effects of influenza on neurosyphilis: 1. The precipitation of profound symptoms in previously latent neurosyphilis by influenza. 2. The augmentation of symptoms and signs of neurosyphilis by influenza. 3. The absence of palpable effect of influenza on the neurosyphilitic process. The latent, incipient, and early cases of neurosyphilis seem to be susceptible to precipitation or augmentation by the added neurotoxic effects of influenza; the advanced cases are not usually perceptibly altered in symptomatology or course. No instances of improvement of neurosyphilis following influenza were observed. The scanty literature is collected and epitomized.

Syphilitic Fever.—Candido Fereira. Parana. Brazil-Medico, 1919, vol. xxiii, p. 97.

The author relates a case as follows: Male, 26 years old, had a series of venereal diseases extending over several years, precise time of syphilitic infection, if any, unknown. On the occasion of a headache he was found to give a Wassermann negative. He was subject to attacks of angina, and in 1918, about 6 years after his diagnostic test, he developed a sore throat with some temperature rise and a general reaction. The diagnosis was grippe, the pandemic having not yet run its course. Fever and headache were very persistent and lasted some weeks without any relief from coal tar derivatives. The angina had long ago subsided. Examined from head to heels nothing could be discovered save a somewhat enlarged liver. An eminent colleague then diagnosticated a possible abscess of the liver with enlargement of the same, and a daily intermittent fever. The blood count was not that of a suppurative process. All possible affections were considered, as acute endocarditis, neoplasm, tuberculosis, malaria, typhoid and paratyphoid fever, suppurative pylephlebitis and influenza sequelæ, all of which were seemingly excluded. A test of an injection of neosalvarsan was followed by a rise of temperature with a positive blood test. The originally negative Wassermanns with the lack of a definite history of syphilitic infection had thrown the medical men off their guard (along with the presence of the influenza pandemic). The history pointed to gonorrhea and chancroids only. In about one month all of the symptoms had disappeared, including the enlarged liver.

The Value of the X-Ray Diagnosis of Bone Syphilis.—Amedee Granger, New Orleans. New Orleans Medical and Surgical Journal, 1919, vol. lxxii, p. 53.

Five cases reported gave histories and presented clinical pictures which justified diagnoses other than syphilis, and in every instance except one the x-ray examination was made to ascertain the extent of the bone or joint involvement and destruction produced by the disease diagnosed, so as to enable a correct prognosis to be made. The syphilitic nature of the infection was not suspected, and it was diagnosed exclusively from the careful study and interpretation of the skiagraphs made, and in spite of all evidence to the contrary, such as negative Wassermann and failure of the usual dosage of mercury and iodides to ameliorate or improve the condition.

Syphilis and Internal Medicine.—J. P. Schneider, Minneapolis. Journal Lancet, 1919, vol. xxxix, p. 338.

In a study, in 1913 and 1914, of the autopsy material of 500 postmortems, the author was impressed with the frequency with which syphilis involved the internal organs. While we have long been duly impressed with the gross pathology of tabes dorsalis, of paresis, and of cerebrospinal lues, and have recently learned properly to evaluate their direct relation to syphilis, we have not been sufficiently alive to the far-from-infrequent syphilitic lesions of the aorta, liver, spleen, heart, larynx, pharynx, bronchial tree, and rectum. From his notes the author finds that in this promiscuous material syphilis of internal organs other than neural tissue and bones, occurred 62 times. It was a revelation to him to find that the aorta was involved in 28 instances. Curiously enough, many of these affected aortas would have been missed by the pathologists themselves ten years ago, because of our lack of understanding that only too frequently atherosclerosis covers and marks the specific media lesions, and that for many years such an infected arch may remain free of distortion and dilation. In these 28 luetic aortas four only were definitely misshapen. We must recognize four possible pathologic and hence clinical pictures, namely: 1. Uncomplicated aortitis. 2. Aneurysm formation. 3. Pure aortic regurgitation. 4. Coronary stenosis. In the 28 instances noted, 14 were of the uncomplicated variety, 4 were grossly dilated; 8 involved the roof of the heart, and spread down over the aortic valve seat, agglutinating the segments and producing a pure aortic regurgitation. Of these 8, 6 died a sudden death. In 2 instances coronary stenosis was present, and classical angina attacks were noted in the clinical record. We must all be impressed with the fact that a blood and spinal fluid Wassermann would be of deciding value in half of the above instances. Clinically, it is well to remember that a patient complaining of a substernal pain in the slightest degree related to exertion needs to be proved clinically, radiologically, and serologically free of syphilis. In contrast with the frequency of syphilis of the aorta stands the infrequency with which the heart itself is involved. In this series only two occcurred: one a gumma of the left ventricular wall, the other of the septum involving the bundle and clinically producing the signs and symptoms of heart-block. Syphilis of the liver occurred 14 times, and, depending upon the age of the individual and the duration of the infection, varied infinitely in pathology from the diffuse parenchymatous of the newborn to the gummatous, perihepatic exudation and cirrhosis of the adult. Contrasted with the Laennec type of cirrhosis hepatis clinically it is well to remember that genuine epigastric and right hypochondriac pain is bitterly complained of in the specific type. Syphilis of the spleen occurred 4 times, in 3 instances in association with the liver lesions, once as a diffuse splenitis, microscopically showing the presence of the spirochete. Destructive gummatous infiltrations of the pharynx occurred 3 times, 2 involving the posterior wall, the third the posterior pillar and soft palate. The larynx was the seat in 4 instances, and in one case was mistaken and treated for tuberculosis. In three individual cases the gummatous process involved the bronchial tree, once in association with cancer, and in the other instances leading to stenosis of large bronchi and death before the nature of the process was recognized. Syphilis of the rectum occurred four times. In but one instance did it lead to death, and that as a result of cancer developing in the stenosed area.

THE DARK-FIELD ILLUMINATION METHOD IN EARLY DIAGNOSIS OF SYPHILIS.—Ralph L. Dourmashkin, New York. Medical Record, 1919, vol. xcvi, p. 234.

The dark-field is the best and the easiest method in early diagnosis of syphilis. It should be used as a matter of routine in all venereal sores or any suspicious open lesion. Where the venereal sore is healed, an attempt should be made to examine the secretion obtained from the inguinal glands. Antiseptic powders or ointments used on a sore render the examination useless. Plenty of strong artificial light, plenty of immersion oil and plenty of moisture on the slide are the necessary factors insuring a speedy and successful dark-field examination. The Spirocheta pallida must be differentiated from Spirochete refringens which is, as a rule, easy. The stained preparations are not reliable.

DEMONSTRATION OF SPIROCHETE PALLIDA IN NERVE TISSUE BY DARK-FIELD ILLUMINATION.—H. B. Shmookler and A. I. Rubenstone, Philadelphia. New York Medical Journal, 1919, vol. cx, p. 107.

The brain and cord of a paretic were immediately removed to the laboratory and by means of dark-field illumination a few Spirochete pallida were demonstrated in the cortex of the frontal, frontoparietal regions, and in the pons as well as the meninges, but only after prolonged search in the latter. As the brain tissue cooled it was more and more difficult to demonstrate organisms, until four hours after death it was utterly impossible. No organisms were demonstrable in the spinal cord and cerebellum. To obtain clear preparations of cortical tissues for dark-field illumination it is essential that the fresh smear from the cut surface of the cortex be mixed with a drop of sterile physiologic saline solution. Inoculation into rabbit testes was made from the fresh material, but the animal was lost due to an intercurrent infection. After prolonged search on Levaditi of many sections, some organisms were discovered, but owing to the great difficulty in differentiating between the other structures that simulate spirochete, these findings would have been of doubtful value without the first dark-field observations. The routine hematoxylon eosin preparations showed not only atrophic changes in cortical cells, but diffuse infiltration with small lymphocytes, with increased amount of fibrous thickening and adhesions of meninges to the cortex.

THE IMPORTANCE OF EARLY DIAGNOSIS AND TREATMENT OF SYPHILIS. John Butler, Minneapolis. Journal Lancet, 1919, vol. xxxix, p. 336.

If the chancre is healed, two drops of a physiologic saline may be injected into its base through a fine hypodermic needle, macerating the tissue by rotating the needle, and aspirating two minutes later a drop or two of saline mixed with serum, which may be collected on a slide and examined for spirochetes. The same procedure may be used for recovering the spirochetes from the enlarged inguinal lymph nodes. There are three methods of spirochete demonstration: staining, India ink, and dark-field illumination. Staining methods for demonstrating the Spirochete pallida have been practically discarded, the objection to this method being: 1. The parasite has a feeble affinity for basic dyes. 2. The long time required for staining it. 3. The organisms are often distorted, therefore, unrecognizable as the Spirochete pallida. 4. Albuminous material or fibrin spirals may be confused with the pallida. 5. A very thin film is necessary. The India-ink method utilizes the fact that spirochetes suspended in India-ink, when the latter is spread out in a thin film, show up as a clear space against a dark background. Thus the Spirochete pallida appears as a white undulating thread, while the film of ink appears yellow or black, according to its thickness. The objection to this method is that the width of the Spirochete pallida varies with the thickness of the films; that in a thick film the spirochetes appear thin; that in a thin film the spirochetes appear thick; that the organism shows great distortion and its undulations are irregular and uneven; and that the important differential sign, motility, is wanting, By the dark-field method a drop of the serum is touched to a cover-glass and immediately pressed firmly on a slide. It is important to see that no air bubbles are included in the film, as they diffuse light. In order to prevent a total reflection of the oblique rays falling on the under side of the slide, it is necessary to put a drop of immersion-oil on the top surface of the condenser and the under surface of the slide. The slide is then placed upon the stage of a microscope, and the condenser racked fully up. The two drops of oil coalesce and fill the air space between. The objective is then lowered (using the high dry lens), the mirror, light, and condenser adjusted, and the oblique illuminating rays are focused in the plane of the preparation where they illuminate the living spirochetes). The spirochetes appear as shining corkscrews, and their characteristic movements may be observed. The parasite is seen to be actively motile, possessing four characteristic movements which differentiate it from other living spirochetes that are morphologically similar. The following movements are noted: 1. Rotation on its long axis. 2. Flexion or bending or lashing. 3. Backward-and-forward motion. 4. Slow progress. 5. Contraction and extension of spirals. 6. Dead-white appearance; other spirochetes show a reddish tinge. The importance of beginning treatment as soon as possible after infection can not be overestimated, for the longer the spirochetes are allowed to multiply in the tissues the more damage is done to them, therefore it is obvious that energetic treatment should be instituted immediately to destroy them and attempt an abortive cure of the disease.

A Rapid Method for Preparing Antigens from Normal Heart Muscle.—E. E. Ecker and K. Sasano, Cleveland, Ohio. The Journal of Infectious Diseases, 1919, vol. xxv, p. 174.

Suitable antigens can be made by extracting normal heart tissues for a period from 1 to 3 hours with boiling alcohol in a reflux condenser. The value of these antigens compares favorably with those extracted by the usual methods. A primary extraction of the dried tissues with ether results in a slight loss of their fixing power, but yields extracts containing less anticomplementary substances.

The Influence of Antigen Dilution on the Wassermann Reaction.—E. H. Ruediger, Bismarck, N. D. Journal of Infectious Diseases, 1919, vol. xxv, p. 224.

The turbidity of the antigen solution and the dilution of the antigen solution greatly influenced the results obtained with the Wassermann reaction with serums from syphilitic persons. For each antigen there seems to be an optimum turbidity and an optimum dilution. Antigen diluted too slowly or too rapidly lost in antigenic value. The optimum dose of antigen would be the proper dose to use in the Wassermann reaction. The optimum dilution of antigen may be somewhat higher than is commonly used; alcoholic extract of human heart gave the strongest positive results in a dilution of 1:50 and alcoholic extract of beef heart and of rabbit heart gave the strongest positive results in dilutions of 1:100. When the antigen was diluted too slowly the optimum dilution of that particular solution was low, and when the antigen was diluted too rapidly the optimum dilution of that particular solution was high; but neither was equal in antigenic value to the optimum dilution of the optimum turbidity. With serums from nonsyphilitic persons the results were uniformly negative.

FROZEN COMPLEMENT IN THE WASSERMANN REACTION.—E. H. Ruediger, Bismarck, N. D. Journal of Infectious Diseases, 1919, vol. xxv, p. 269.

Frozen guinea-pig complement one week old, whether composed of the mixed serums of 3 guinea-pigs or of the serum from one guinea-pig usually gave a little stronger positive results with the Wassermann reaction than did the same complement while fresh. At the age of 2 weeks the frozen complement gave results that were nearly identical with the results obtained with the fresh complements. After 2 weeks the frozen complement gradually lost strength which seemed to be more rapid in mild weather than in very cold weather.

THE COLLOIDAL GOLD REACTION IN FOUR HUNDRED AND NINETY-EIGHT PSYCHIATRIC CASES.—Eva Rawlings, Kalamazoo, Michigan. Archives of Neurology and Psychiatry, 1919, vol. ii, p. 180.

The spinal fluid of cases of dementia paralytica causes a quite characteristic curve with the colloidal gold solution which is of such frequent occurrence as to be diagnostic. Seven of the author's cases were confirmed necropsy. The spinal fluid of taboparetics may normally give syphilitic curves or low paretic curves as evidenced by the reactions of a number of paretics and as confirmed by necropsy. Cerebrospinal syphilis gives a curve which may be considered diagnostic. Syphilitic curves with negative Wassermann reactions of serums and spinal fluids may be obtained in cerebrospinal syphilis having been demonstrated pathologically in five cases, the reaction not necessarily being due to a dialyzable substance other than syphilitic. The gold curve is of value in clearing up the etiology of old arteriosclerosis with negative Wassermann reactions; necropsy having demonstrated a syphilitic type of vascular lesion in cases giving syphilitic curves and a simple senile degeneration of the vessels in cases giving negative gold reactions. It is of interest that five cases of Huntington's chorea gave negative gold reactions, one of which however, demonstrated pathologically an inactive moderate tabetic involvement of the lumbar regions. The syphilitic curve may be of value in clearing up the etiology of mental deficiencies after an active syphilitic process has ceased and antibodies have disappeared from the body fluids. The globulin reaction is rather uniformly strongly positive in paretics and a fair proportion of syphilitics, but there appears to be no definite relationship between the curve and the strength of the reaction.

DIAGNOSIS AND TREATMENT OF SYPHILIS.—Loretta Joy Cummins, Boston. Boston Medical and Surgical Journal, 1919, vol. clxxxi, p. 166.

One positive Wassermann does not necessarily mean lues any more than one negative means that a person has not lues, or that a treated case is cured. The laboratory test is a most helpful aid in making a diagnosis and in checking up a case under treatment, but it is not infallible. The dark-field illumination furnishes a valuable means of corroboration in all suspicious genital and extragenital lesions, and the diagnosis of chancroid should not be positively made without this examination to exclude the possibility of a coincident infection with the Treponema pallidum, for it is well known that the soft sore frequently harbors the parasite of syphilis. The secondary cutaneous eruption may be of all types from macules to nodules. The color is brownish red, or is often described as ham color. The eruption occurs in characteristic groups, in circles or segments of circles, is generalized and bilateral. It is often more abundant on the forehead, around the nose and mouth, front of the trunk, and on the palms and soles. The multiformity of lesions is quite characteristic of syphilis, as is the absence of subjective symptoms of itching, burning, and pain. One of the greatest advances made in our knowledge of syphilis is that involvement of the central nervous system takes place in the secondary stage. It is, therefore, most important that the physician should study his patient closely, and be keen to observe beginning eye changes or other signs of central nervous system involvement. Unless there is some special indication for it, lumbar puncture should not be made until the patient has had at least one course of salvarsan. If, on first examination, the Wassermann reaction is found to be strongly positive with 0.4 or 0.2 c.c. of fluid, the combination of intravenous and intraspinal treatment should be started at once. The treatment generally used is the Swift-Ellis-Ogilvie. The management of a case of syphilis should not be in the hands of the general practitioner, for, while he may be able to clear up all physical signs of the disease, he is not capable of assuming the great responsibility of a cure. The advances made in the treatment of syphilis have been so great that even specialists today must be very alert in order to be up to the minute.

Differential Diagnosis in Nervous Syphilis.—W. A. Jones, Minneapolis. Journal-Lancet, 1919, vol. xxxix, p. 342.

A physical examination usually shows some of the cardinal differential points. In syphilis the pupils are usually different in size and in form; and a pupil that is irregular, elliptical, or larger than its fellow, is very suggestive of a syphilitic origin. Some one has said that the left pupil is more apt to be larger than the right. When a fixed pupil exists, and the knee-jerks are unobtainable, or are obtained only with great difficulty and by reinforcement, one must immediately consider the possibility of a developing tabes, a posterior spinal sclerosis. The usual methods of diagnosticating tabes will clear up any uncertainty that one may entertain. But, again, if this condition is associated with alcoholism, with its stupor and mental phases, due to a wet brain, further investigation may be needed to determine the relative value of the two disorders. One precaution may be sounded as to the value of the blood Wassermann and the spinal-fluid Wassermann. One must be prepared for an occasional uncertain diagnosis, for in both of these diseases (alcoholism and nervous syphilis) there is a tremor, usually of the extremities or of the tongue, and the safest method in differentiation is a spinal puncture with notation of the pressure of the spinal fluid, and the reaction obtained for syphilis, as well as a positive globulin and excess albumin. When the neurologic symptoms predominate, however, and there is a persistent tremor or a persistent special defect shown by the alteration of the reflexes, and particularly the defective reflex in the pupil, the probabilities are that syphilis is the fundamental cause of the disease.

NEUROSYPHILIS.—Philip Goldfader, Brooklyn. New York Medical Journal, 1919, vol. cx, p. 278.

The pathologic changes that occur in syphilis of the nervous system may be classified under four headings: 1, Meningeal neurosyphilis; 2, vascular neurosyphilis; 3, parenchymatous neurosyphilis, and 4, combinations of the first three, as: a, meningovascular neurosyphilis; b, meningoparenchymatous neurosyphilis; c, vasculoparenchymatous neurosyphilis, and d, meningovasculoparenchymatous neurosyphilis. The symptoms usually found in patients with syphilis of the brain are as follows: headache, alteration of personality, paralysis of the cranial nerves, insomnia and disorders of motor function. The symptoms and signs of spinal cord lesions due to syphilis are Romberg sign, absent knee jerks and Achilles tendon reflex, lancinating pains, staggering gait, Argyll Robertson pupil, sphincter disturbances, sensory disturbances, visual disturbances, paresthesia and numbness of feet and lower extremities, girdle sense, loss of sexual desire, Charcot joints, hemiplegia and deafness. The indications for lumbar punctures in cases of syphilis are: 1. All cases coming under observation after the primary stage has passed as a diagnostic procedure. 2. Patients who have been under active treatment for eight to twelve months, with no improvement in the blood Wassermann. 3. As a therapeutic agent to relieve severe headache in cases of cerebral syphilis. 4. To differentiate between involvement of the nervous system of syphilitic and of nonsyphilitic origin. 5. To introduce medicaments into the spinal canal. 6. Examination of the cerebrospinal fluid as a guide in treatment. 7. As a diagnostic measure before discharging a patient as cured. There are three methods of administering salvarsan in the treatment of syphilis of the nervous system, namely: intravenously, intraspinally, or a combination of both. Intravenous administration of salvarsan can be employed in early cases of cerebrospinal syphilis (meningitis, meningomyelitis, meningoencephalitis), early cases of tabes, syphilitic epilepsy, and secondary cases of syphilis showing involvement of the cerebrospinal fluid without nervous symptoms. The intravenous administration of salvarsan should be first tried in these classes of cases, for the improvement both clinically and serologically is fairly rapid under intensive treatment. Patients not influenced by intravenous injections of salvarsan combined with intramusclar injections of mercury and internal administration of iodides, should then receive both intravenous and intraspinal injections of salvarsan. While the intraspinal treatment of syphilis of the nervous system can be employed in all forms of the disease, it is in the parenchymatous types in which it has its greatest field of usefulness, especially in cases of tabes and paresis. In these latter cases the author employs a combination of intravenous and intraspinal injections.

ONE ASPECT OF SYPHILIS AS A COMMUNITY PROBLEM.—H. S. Newcomer, Russell Richardson and Charlotte Ashbrook, Philadelphia. American Journal of the Medical Sciences, 1919, vol. clviii, p. 141.

The author's experience shows that it is practicable for any well-organized general hospital to establish a clinic for the treatment of syphilis without great expense to the institution and to the certain advantage of the community it serves. The fundamental questions of morality which underlie the spread of this infection do not properly present themselves for the consideration of the physician and the hospital in connection with such a clinic. The practice of segregating the syphilis clinic from the more general work of the hospital, which has been so general, should be abandoned, as it makes the treatment appear to the patient in the light of punishment and to the hospital staff and management as a disagreeable duty. The interests of all are thus sacrificed to sentiment, and in the confusion the propaganda for better morals is not effectively advanced. Medically speaking, their results confirm the prevailing view that once syphilis has invaded the body it is very difficult if not impossible to eradicate. Systematic treatment is, however, capable of minimizing its effects for the individual, and at the same time rendering him almost innocuous to the community. Such a clinic as this is probably more successful in securing treatment in this systematic way than is management by the private practitioner. It being assumed that such clinical facilities as those described have been made available in adequate amount, the attack on syphilis as a community problem should involve as a measure of the first importance systematic effort to secure treatment at the earliest possible moment for those infected.

INTENSIVE ARSPHENAMINE THERAPY.—H. H. Hazen, Washington, D. C. Southern Medical Journal, 1919, vol. xii, p. 371.

While the three-day interval is not advocated as the only method to be employed, or even as the ideal method, yet it has been demonstrated that a patient will stand as many as ten injections at seventy-two-hour intervals with perfect impunity, that much time is saved, and that both clinical and serologic conditions are brought to normal in a much shorter space of time than is possible with injections given but once a week. So far as ultimate results are concerned, it is still too early to say just what will take place, but so far the observations are encouraging.

THE PRIMARY TOXIC EFFECT OF NEOSALVARSAN.—Professor K. Petren, Lund, Sweden. The Lancet, 1919, vol. cxcvii, p. 245.

From the description we find that the toxic effect after the injection of salvarsan was quite monosymptomatic, and that the only toxic effect, when it occurred at all, followed fixed laws, as its occurrence was limited to a fixed period after the injection and was also to a certain degree dependent on the weight of the individual that had received the injection. When we take these circumstances into consideration it seems unnecessary to discuss the question where the injected salvarsan exercises its effects, as it is quite manifest that a morbid phenomenon of this regular character and of this short duration (with no exception from the rule that the vomiting occurs only during the first 24 hours after the injection) can not be the consequence of a local effect exercised on the stomach wall, but must be the effect of the poison on the center of vomiting in the bulb. In consequence, thanks to the circumstance that the author's observations on the effect of the injection of salvarsan are uncomplicated, in the sense that they are free from the disturbing influence of the biologic effect exercised by salvarsan on the microorganism of syphilis, and thanks to the fact that these observations are of sufficiently great number to lead to the deduction that the phenomena produced are governed by certain laws, we come to the conclusion that the first toxic effect of salvarsan (neosalvarsan) on man can be demonstrated with certainty of an experiment on animals, and that this toxic effect consists in a strictly elective effect produced exclusively on the center of vomiting in the medulla oblongata.

DESTRUCTIVE ACTION OF NEOSALVARSAN ON LEUCOCYTES.—Harry Lowenburg, Philadelphia. New York Medical Journal, 1919, vol. cx, p. 326.

The marked reduction in white cells, red cells, and hemoglobin is noted in a case of acute lymphatic leucemia. Whether this was dependent upon the action of large doses of arsenic as represented by neosalvarsan, or whether it represented a prelethal phenomenon is a matter for discussion. The former conclusion seems inevitable inasmuch as the reduction in white cells occurred almost immediately after the systemic introduction of the drug and also because arsenic in poisonous dose is known to be hemolytic in its effect. Furthermore, the natural history of leucemia records a marked spontaneous reduction in the white cells only as an immediate preagonal phenomenon, or as the result of an acute intermittent infection, for example, in tonsillitis. The latter was absent and the reduction was noted at least a week before death, and, as was stated, immediately following the use of the drug. The query as to whether a too large amount of arsenic was introduced is, of course, relevant and can only be determined by noting the effect of smaller doses when the opportunity for their employment will present itself in a subsequent case. Aside from the main point of interest in the protocol of this particular case, viz., the effect of neosalvarsan on the reduction of the blood elements, the conclusion must be accepted that thus far the medical profession remains in darkness as to the cause and cure of this disease.

NOTES ON THE EFFECT OF INTRAVENOUS DIARSENOL.—W. C. Rappleye, Foxborough, Mass. Journal of Laboratory and Clinical Medicine, 1919, vol. iv, p. 630.

It seems quite evident that the fragility of normal red cells is not altered by diarsenol introduced directly into the blood stream. Such a conclusion, however, does not warrant a statement that in the abnormal blood conditions, such as the hemolytic anemias, the introduction of arsenical compounds into the blood stream does not increase the resistance of the red cells. In the group of cases noted, it will be seen that the introduction of diarsenol into the blood stream affects the urea values but little, if any. The variations are within normal range. It is true that there is a slight majority of the cases which showed a drop rather than a rise in values during the first few hours after the injection. But the drop is not conclusive, surely not as striking as the drop in blood urea nitrogen noted in catatonia and reported in another connection.

THE WASSERMANN REACTION IN SYPHILIS AS A GUIDE TO TREATMENT, W. D. Sutherland and Rai Gopal Chandra Mitra Bahadur, Calcutta, India. Indian Medical Gazette, 1919, vol. liv, p. 201.

The authors have been struck by the number of cases in which the Wassermann reaction was not easily and favorably affected by treatment because the physician in charge of the case had pushed organic arsenic compound, but neglected mercury as a means of treatment. Organic arsenic compound alone can do much and mercury can do much alone; but neither organic arsenic compounds nor mercury when given alone can do half as much as the two combined can accomplish. This was pointed out by Ehrlich in 1911, and the more syphilitics they see the more convinced are they that the fact should be known to all who have to treat them. With diffidence they mention that it seems to them that the best results have been obtained by using mercurial inunctions in preference to intramuscular injections or pills.

Some Notes and Observations on Syphilis.—H. E. Michelson, Minneapolis. Journal Lancet, 1919, vol. xxxix, p. 374.

The dark-field is essential for all early diagnosis of chancre, and the discovery of the specific spirochete in a lesion is indisputable proof of luetic infection. The Wassermann reaction can not be obtained earlier than the thirty-fifth day, and it is an unpardonable error to wait for a positive Wassermann in early infected cases. Abortive "cures" are possible if the infection is discovered before general systemic infection has taken place, that is, before a positive Wassermann. In treatment, the individual must be treated as well as the disease. Competent consultation must be sought when special tissues are involved, such as the aorta, the nervous system, the eyes, etc. A Wassermann rendered negative is no proof of a cure, the sum total of treatment over a sufficient length of time being essential.

Syphilis and the General Practitioner.—Albert T. Lytle, Buffalo. New York State Journal of Medicine, 1919, vol. xix, p. 96.

The fate of the syphilitic depends upon the early diagnosis of the infection and the intensity with which the treatment is carried out during the first six to twelve months. Persistence in the treatment should run parallel with the persistence of the Wassermann reaction. There is really only one remedy, and that remedy is mercury. Early in the primary stage it is possible to obtain a cure with one dose of the arsenic preparation, salvarsan; but even so, it is infinitely better to administer mercury for six months following the administration of five to ten doses of salvarsan. In the secondary phase the system should be saturated with mercury both before, during and after interrupted intravenous administration of massive doses of salvarsan. After a year of practically continuous mass attacks, periods of rest may alternate with the administration of the remedies over an additional one or two years, depending upon the Wassermann findings. To the treatment with mercury and arsenic in the tertiary phase is added iodine for its resolvent effect; thereby the pill box machine gun nests of the Spirocheta pallida are broken up and it becomes amenable to the action of the other remedies.

STANDARD SYPHILIS No. 1.—Major J. Bayard Clark, New York. New York State Journal of Medicine, 1919, vol. xix, p. 282.

The title of this paper has been used to designate the formula employed in the treatment of all early and uncomplicated cases of syphilis during the last six months at the Base Hospital at Camp Logan, while the Genitourinary Service has been under the direction of the writer. Each patient to be carefully scrutinized for signs of stomatitis or general malaise, his weight to be taken; and his urine tested before each injection and after it. In conjunction with the employment of this course of treatment each Medical Officer shall be familiar with "Proposed Modification of Circular No. 14, W. D., Office of the Surgeon General." Patients are to be treated at Base Hospital until open lesions are healed, when they will be sent to Development Battalion or Regimental Surgeon for completion of treatment. The scheme of arsphenamine dosage is based on 150 pound men, or one decigram to about 30 pounds body weight.

	Arsphenamine (Intravenously)	Hg. Salicylate 33% in Olive Oil (Intramuscularly)
1st day	gm. 0.3	grain 1.
6th day	gm. 0.4	grain 1.
11th day	gm. 0.4	grain 1.
18th day	gm. 0.6	grain 1.
25th day	gm. 0.6	grain 1.
32nd day	gm. 0.6	grain 1.
39th day	gm. —	grain 1.
46th day	gm. —	grain 1.5
53rd day	gm. —	grain 1.5

One month rest, then take Wassermann; if positive, repeat entire course; if negative, repeat the Hg alone. At end of second course, rest two months, then take Wassermann and give third course in accordance with rule for second course. During second year, if Wassermann is positive, repeat entire courses as above. If negative, give two Hg courses with four months between.

GENERAL PARALYSIS TREATED BY INTRAVENTRICULAR INJECTION OF ARSPHENAMINE.—Irving J. Sands, Brooklyn. Archives of Neurology and Psychiatry, 1919, vol. ii, p. 41.

A man, aged 40, married, who had one living child, a negative family history, but an alcoholic personal history, who had no knowledge of any venereal disease, began to show lapses of memory in December, 1915, which increased in severity so that he was obliged to discontinue his work as a carpenter in the middle of 1916; he then became irritable, showed speech defect and became ataxic; in March, 1917, he received one intraventricular injection of arsphenamine through a trephined opening in the skull. He was admitted to the Manhattan State Hospital in May, 1917, when he showed disorientation, poor memory, expressed grandiose ideas; showed marked speech defect, pupils were unequal and reacted very sluggishly to light, and the spinal fluid showed positive globulin, 54 cells, and a positive Wassermann reaction. He soon began to soil himself, became very euphoric and died following a convulsion. The postmortem examination showed the characteristic lesions of general paralysis in the brain; namely, a thickened pia showing a characteristic milky exudate in the anterior poles of the cortex, lymphoid and plasma cells infiltration into the pia, neuroglia increases, cortical disorganization and perivascular exudation of lymphoid and plasma cells, many mast cells and a few rod cells, granulations on the floor of the ventricles, syphilitic aortitis and bilateral bronchopneumonia and pulmonary edema; the lesions in the left side of the brain which received the arsphenamine were more intense than those in the right side.

TREATMENT OF NEUROSYPHILIS BY ARSPHENAMINE INTRAVENOUSLY AND AUTO-ARSPHENAMIZED SERUM INTRASPINALLY.—George M. Goodwin and J. R. Scott, New York. Archives of Neurology and Psychiatry, 1919, vol. ii, p. 59.

In this series of cases 214 intraspinal treatments have been given. Severe reactions have occurred, but the authors have seen no permanent injury or ill effects result from the intraspinal use of auto-arsphenamized serum. The treatment has uniformly been of benefit in its effect of increasing the patients' comfort by lessening the severity and frequence of their pains, in frequently improving bladder control, and in improving their nutrition. Improvement in station and in gait has frequently been observed in these cases, and in some, to a very marked extent.

OBSERVATIONS ON INTRASPINAL AUTO-ARSPHENAMINIZED SERUM TREATMENT OF CEREBROSPINAL SYPHILIS.—B. A. Thomas, Philadelphia. The Pennsylvania Medical Journal, 1919, vol. xxii, p. 377.

It is not claimed that arsphenamine therapy, either intravenously or intraspinally, can restore degenerated spinal cords or rescue victims from impending institutional care. Although many patients, even tabetics, respond to general or intravenous treatment, the accessory employment of intraspinal treatment accelerates the restoration of the spinal fluid to normal, arrests the degenerative process and insures greater permanency of therapeutic results. Intraspinal treatment by auto-arsphenaminized or arsphenaminized auto-arsphenaminized serum injections should supplement intensive intravenous therapy only when necessary. Cases of endarteritis with vascular or circulatory disturbances and those with exudative gummatous meningitis, also many cases of tabes dorsalis, respond satisfactorily to intravenous therapy alone. Cases with marked tract or cortical degeneration offer little if any hope of improvement by this or any other known method of treatment. Treatment in qualified cases should be continued until the findings in the spinal fluid, as well as the blood, are rendered negative, except globulins, which may persist positive in many cases irrespective of the amount of treatment. Mercury and the iodides continue to be indispensable supplementary therapeutic agents in the treatment of cerebrospinal syphilis.

THE TREATMENT OF NEUROSYPHILIS.—A. W. Morrison, Minneapolis. Journal-Lancet, 1919, vol. xxxix, p. 344.

The important points in treating all forms of neurosyphilis are to get the patient early, to give energetic and prolonged medication, preferably, and certainly at first, by intravenous injections of arsphenamine combined with mercury and the iodides, and not to be satisfied with a symptomatic cure alone. Therefore, not only should the treatment be controlled by repeated examinations of the spinal fluid, but, even after the patient is pronounced cured, he should be kept under observation for several years, and the reactions of his spinal fluid followed, as well as observed clinically.

THE MALONEY METHOD IN THE TREATMENT OF ATAXIA.—Morris Grossman, New York. Medical Record, New York, 1919, vol. xcvi, p. 268.

The method of treating tabetic ataxia that Maloney has elaborated is based upon the thesis that perfect thinking is essential to perfect moving; and that perfect moving is the outward sign of perfect thinking. The mental state, fatigue, and fear, Maloney combats with "rest exercises;" and lastly he has introduced blindfolding into his method as a measure to decrease external distraction, thereby allowing greater concentration and more intensive application for interpreting the delayed, imperfect, postural images that result from interference in conduction of sensory stimulæ. Of the 15 cases reported here, 10 received antispecific treatment either at the time when they had their chancre, or at a later date when involvement of the cerebrospinal axis was probably evident. Some of these patients had received what might be considered adequate treatment, or nearly adequate, both at the time of their primary infection and at a more recent date; yet the disease, with the exception of slight evanescent improvement in some of the symptoms, relentlessly progressed. In others there was no improvement, and in some aggravation of the symptoms was definite. While receiving this mental treatment, with the exception of 2 cases, no salvarsan or mercury was given. The length of time devoted to each patient was governed by his mental and physical capacity for work, the average being about one hour four or five times a week. The average length of time required to cure the ataxia in this group of cases was 8 to 12 weeks. This period can be considerably shortened by intensive treatment. With this method of treating ataxia, the author was able to return to a nonataxic state, 12 of the 15 cases here reported. Most of these patients are still in a nonataxic state or were so when last seen or heard from. Nearly all were able to go about in public without aid; a few could not be induced to give up their stick when in public, but could get along without any aid from it. It has been a remarkable feature in all of these patients, that their attacks of pain and their crises, have been much reduced in frequency and severity during and since the treatment has been given. The possibilities that this method of treatment offers to the unfortunate victim of tabes for relief of his most distressing symptoms, namely, ataxia, pain, and crises, are indeed gratifying.

BOOK NOTICES

(Books for review should be sent to Dr. W. H. Deaderick, Associate Editor, Dugan-Stuart Bldg., Hot Springs, Arkansas.)

An Outline of Genitourinary Surgery.—By George Gilbert Smith, M.D., F.A.C.S., Genitourinary Surgeon to Outpatients, Massachusetts General Hospital. 12mo. of 301 pages with 71 illustrations. Cloth $2.75 net. Philadelphia and London, W. B. Saunders Company, 1919.

The author states that this book has been written with the idea of presenting to students and to general practitioners the important points in the symptomatology and pathology of genitourinary diseases. The treatment of these conditions, in so far as it deals with medicine or with minor surgery, is given in full; when major surgery is indicated, enough of the technic is described to give the medical reader an intelligent opinion as to the nature of the operation, its aims and its dangers. The methods and technic described are those which the author in his own experience has found valuable, thus giving his suggestions practical worth. At the end of each chapter have been added references representing the views of men of authority upon the subject under discussion. The illustrations are profuse and original and the general make-up of the book excellent. As a practical working manual this work can be very highly recommended, not only to the specialist, but to the general practitioner.

Diseases of the Skin.—By James H. Sequira, M.D., Lond., F.R.C.P. Lond., F.R.C.S. Eng. Physician to the Skin Department and Lecturer on Dermatology at the London Hospital; in charge of Queen Alexandria's Department for Light Treatment; Honorary Consultant for Diseases of the Skin to Military Hospitals in London; Consulting Dermatologist to the Radium Institute; Secretary of the British Section of the International Association of Dermatology and Syphilology; Fellow of the Royal Society of Medicine; formerly Physician to the North Eastern Hospital for Children. 644 pages. Third edition with 52 plates in color and 257 text figures. Cloth $12.00 net. Philadelphia, P. Blakiston's Son and Co., 1919.

This work had its inception with notes for a course on lectures delivered in the Skin Clinic of the London Hospital in 1902 and has gradually grown with the author's experience of nine years' teaching. Special attention is devoted to diagnosis and treatment omitting historical references and discussions of debated points. A general arrangement of the chapters is on etiologic lines, a system which modern developments have rendered possible, though still incomplete. Where such a classification has been impracticable, the diseases are grouped according to their morphologic characters. The author has exercised great care in the selection of the illustrations, which, with a few exceptions, are original. The colored plates are excellent, and the black and white illustrations, usually unsatisfactory in dermatologic works, are unusually good. The table of contents includes: histology and functions of the normal skin, morphology, congenital affections of the skin, eruptions due to local irritation, eczema, affections caused by animal parasites, affections caused by vegetable parasites, microbic affections of the skin, syphilis, exotic spirochetal diseases and leishmaniasis, eruptions caused by drugs, vaccines and antitoxines, cutaneous affections in general and visceral diseases, toxic eruptions, the erythrodermias, affections dependent upon vascular and lymphatic obstruction, etc., neurodermatoses, erythemato-squamous eruptions of unknown origin, papular eruptions of unknown origin, follicular keratoses and allied conditions, the pemphigus group, leucodermia, melanodermia and chloasma, atrophy and sclerosis of the skin, tumors of the skin, diseases of the appendages. About 60 pages are devoted to the subject of syphilis and the author's consideration of this subject is sane and practical. The book can be unqualifiedly recommended to those interested in dermatology and syphilology.

THE PRACTITIONER'S MANUAL OF VENEREAL DISEASES (WITH MODERN METHODS OF DIAGNOSIS AND TREATMENT).—By A. C. Magian, M. D., Hon. Surgeon Manchester French Hospital; Hon. Surgeon Wood Street Clinic for Genitourinary Diseases; Lecturer on Venereal Diseases, Post-Graduate Clinic, Manchester, England. 210 pages, with 60 illustrations. Cloth $3.00. St. Louis, C. V. Mosby Co., 1919.

The author has written this book especially for the general practitioner. It contains a concise outline of the diagnosis, symptoms, and treatment of venereal diseases as we are acquainted with them today. Elaborate microscopic and chemical tests and operative procedures, which only serve to enlarge the text and confuse the reader, have not been incorporated.

The book contains chapters on Gonorrhea, Complications of Gonorrhea, Various Forms of Gonorrhea, Treatment of Gonorrhea, Gonorrhea in Women, Social Considerations, Proofs of Cure, Prophylaxis, Chancroid (Soft Sore), Syphilis, Syphilis of Various Systems, Hereditary Syphilis, Treatment of Syphilis, Locomotor Ataxia, Syphilis and Marriage, Instructions to Patients.

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